Congress of the United States
Office of Technology Assessment

LOSING A MILLION MINDS: CONFRONTING THE TRAGEDY OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Contractor Documents

Part 1:
Epidemiology, Diagnosis, and Basic Science

March 1987

The Epidemiology of Dementing Disorders, Peter S. Cross and Barry J. Gurland, The Columbia University Center for Geriatrics, Gerontology and Long-Term Care, New York, New York 10032

Accuracy of Diagnosis and Consequences of Misdiagnosis of Disorders Causing Dementia, Robert Katzman, Bruce Lasker and Nancy Bernstein, School of Medicine, University of California, La Jolla, California 92023

Basic Neuroscience and Disorders Causing Dementia, Donald L. Price, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2182

These are contractor documents that were used in preparing OTA's final Assessment Report. OTA makes these contractor documents available for the use of readers desiring a more detailed or technical discussion of an issue than can normally be accommodated in our final Report. As an OTA contractor documents, they have not been reviewed or approved by the Technology Assessment Board. The findings and conclusions expressed are those of the authors and do not necessarily reflect the views of OTA, the Advisory Panel or the Technology Assessment Board.

J952-18

This document can be ordered in either paper or microfiche format from:

National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22161
Tel: (703) 487-4650
Telex: 89-9405

January 1986

THE EPIDEMIOLOGY OF DEMENTING DISORDERS

A Report on Work Performed For
and Submitted to
the United States Congress,
Office of Technology Assessment

Peter S. Cross, M. Phil.

Barry J. Gurland, F.R.C. Psych.

The Columbia University Center for Geriatrics,
Gerontology and Long-Term Care, of
The Faculty of Medicine
College of Physicians and Surgeons
New York State Office of Mental Health

New York, New York 10032

CONTENTS

Introduction 4

- Uses and purposes of epidemiology 6
- Elements of the prevalence survey 6

The Dementia Syndrome 11

- Boundaries 11
- Subtypes of dementia 13

Epidemiologic Studies 21

- Variations in population studied
- Variations in case-finding
- Care ascertainment methods
- Adjusted prevalence rates
- Occurrence in the non-elderly
- Sub-types of dementia
- Is prevalence rising?
- The increasing burden of care

Epidemiologic Research 48

- Recent federally supported studies
- Recommended studies

Appendices

- A. Recent and on-going federally-funded studies in the epidemiology of the dementias 51a

References 52

LIST OF TABLES

1. Criteria for Diagnosis of Non-Specific Dementia 12
2. Epidemiologic Surveys ... Area Studied, Type of Population Sampling, Ascertainment Methods 22.
3. Epidemiologic Surveys: Prevalence of Severe Dementias 28
4. Adjusted Estimates of Total Prevalence of Dementia in the Elderly Population 32.
5. Epidemiologic Surveys: Prevalence in the Non-Elderly 34.
6. Epidemiologic Surveys: Subtypes of Dementia 35.
7. United States 1950-2040: Population, Cases of Dementia, Prevalence of Dementia, and Percent of Cases in Oldest Age Group 41.

LIST OF FIGURES

1. Decision Tree for Diagnosis of Dementia 14

2. Age-Specific Prevalence Rates of Dementias Found in Various Studies 39

3. Projected Cases of Established Dementia in the United States 40

4. Contribution of Elderly Age Groups to Projected Increase in Cases of Established Dementia 42

5. Familial Dependency Ratio (Population Aged 80+ as a Proportion of Those 60-64) 47

6. Societal Dependency Ratio (Population Aged 65+ as a Proportion of Those 18-64) 47.

INTRODUCTION

The large increase in both the number and proportion of elderly in our population together with the steep increase in incidence of the dementias with increased age has resulted in sharply increased prominence of the dementias. Each new case affects most dramatically family members and friends who bear the brunt of the care, and also affects a widening circle of acquaintances and health professionals, and, in the end, becomes a matter of concern for the public who at a minimum share the large and growing public costs due to these diseases.

The elderly constitute eleven percent of the national population but account for about a third of all expenditures (and about half of all public expenditures) for health care (Fisher, 1980).

Studies of the community-resident elderly have repeatedly found that the demented use a large proportion of health and personal social services. Gurland et al. (1980) in a study of a probability sample of elderly New Yorkers living at home found that of the tenth of the sample most dependent on others for help to survive in the community, nearly half had dementia as a primary reason for this dependency. Akhtar's (1973) report of a study of community-resident elderly in Northern Scotland found that of the most dependent 3.5% of the sample, over three-quarters were demented.

In the Newcastle-upon-Tyne study (Kay et al., 1970) the 6% of the sample of the community-resident elderly diagnosed as demented, upon several years follow-up, accounted for over half of all time spent by the sample in residential homes and nearly a third of all hospital admissions. (This despite their considerably greater mortality during the follow-up period.)

Studies of the elderly in institutions tell the same story. Over two thirds of all elderly residents in state and county mental hospitals and half of all elderly admissions have a primary diagnosis of "chronic organic brain syndrome" (Millazzo-Sayre, 1978; Meyer, 1977). Estimates of the prevalence of dementia in nursing homes range from over a third to two thirds (German & Kramer, undated; National Center for Health Statistics, 1979; Gurland et al., 1979).

Problems in the provision of care to the demented have added to these concerns. Caregivers see themselves as confronted with an unsympathetic system of medical and social supports and have formed active groups for self-help to advocate for more responsive social and medical care and for increased research. Nursing homes have been a source of concern due both to poor care in some and due to rapidly increasing costs both to individuals and government.

These concerns are heightened further by the knowledge that the elderly population is growing and that the dementias will become a problem of even greater magnitude. Attempts to deal with the problem range from basic research, to treatment approaches, to attempts to ameliorate the widespread costs, be they the social, psychological or economic.

Here we review the epidemiological contribution to these efforts with special emphasis on the contribution to public policy making.

Uses and Purposes of Epidemiology

Epidemiology studies diseases as they occur among (epi) the population (demos) seeking to describe the ocurrence and distribution of the disorder in the population and thereby to clarify the causes of the disease (MacMahon & Pugh, 1970).

Descriptions of the occurrence and distribution are of great import for other scientists and for policy makers, planners, administrators and service providers. The frequency of the dementias (and of particular kinds of dementia) in the general population, in specific population groups (e.g. by age), and in particular settings may shed light on:

- causes of the dementias
- precipitating or aggravating factors
- present and projected needs for people and programs to provide services to victims and their families.
- groups at high risk for these disorders
- frequency of unrecognized or inadequately treated cases
- the costs of the disorders, public and private, economic and non-economic

Elements of the Prevalence Survey

All epidemiologic surveys seeking to describe the frequency and distribution of dementia (or some type of dementia) face in common questions about how the study is to be done. These questions of method are not matters of trivial detail but importantly affect the study results. Here we set out a brief overview of major considerations of method:

- o how the population to be studied is selected
- o how a 'case' of dementia is to be defined
- o what the information needed is to define a case and how this is to be collected
- o what measures of occurrence and distribution should be used

Selecting the Population

The prevalence survey generally covers all individuals within a geographical area. Some studies are limited to individuals at risk, (those above some specified age, say 60 or 65, below which dementias are deemed sufficiently rare).

Some surveys may include only individuals living in the community (omitting individuals in acute care hospitals, or mental hospitals, or nursing homes); other studies have been of only those living in such institutions. While such studies are acceptable for some purposes, they are not useful in estimating overall prevalence since, indisputably, substantial portions of demented subjects reside both in the community and in institutions.

In some instances (small communities) it may be possible for the investigators to survey every (or nearly every) individual at risk, that is to take a complete census. In other instances the population may be sufficiently large (in relation to study resources) that only a sample of the population can be taken and in such instances, the sample must be drawn according to (sometimes complex) known methods of ensuring that the sample truly reflects the entire population of interest.

Equally important are ensuring that the study adequately assesses all individuals in the sample, not only those who are available, or cooperative, or in good health.

Defining a Case

There are varieties of dementia, varieties of diagnostic and classifying systems, varieties of ways of operationalizing these within an epidemiologic study. These are of great consequence and hence are discussed is some detail later.

Here we mention two quite general requirements that need to be met. First, those identified by the study procedures as "cases" must (preferably to some known extent) be 'cases' -- the case definition must be valid. Secondly, the set of procedures and definitions resulting in the identification of a case must be replicable, repeatable -- case definition must be reliable.

The validity of case definition in studies of dementia is especially problematic since there is no infallible method of diagnosing the most common types of dementia even under ideal conditions. There is no abolute correct standard. Furthermore, the purposes of the study may indicate the use of different standards: a study aimed at describing the service needs of the demented might well define cases by level of severity as seen in need for personal assistance; a study focused on possible interventions might focus case definition on the distinction between reversible dementias and the progressive dementias; an etiologic study of Alzheimer's disease would place great emphasis on accurate sub-typing of dementia.

Reliability is sometimes spoken of incorrectly as a property of the diagnostic instruments (measures). While this is in part so, reliability depends as well on characteristics of the population being studied and depends critically upon sytematic case assessment methods and competent and motivated assessors. Assuring that methods found (e.g. in a special sub-study) to be reliable are maintained through the entire study is necessary to obtain accurate results.

Measures of Occurrence

The usual measure of frequency used in prevalence studies is the prevalence rate which is simply the ratio of cases to the population at risk usually expressed in terms of some conventional population size (e.g. 5 per 100 or 5%; 50 per 1000; 500 per 10,000). Prevalence is for a specified time period: it may be "point prevalence" based on the number of cases and population at one moment in time or "period prevalence", the number of cases that exist or existed over one month (or year, 10 years, a lifetime, whatever). The period of time selected can make a small or large difference in the rate. For a chronic (i.e. unremitting) progressive disease, such as Alzheimer's, the difference between point prevalence and one-month prevalence would be small; whereas for, say, acute confusional states (typically short in duration) the difference between point prevalence and one-month prevalence could be substanital.

Nearly all epidemiological studies of dementia report such prevalence rates but it is useful, at least conceptually, to view the prevalence rate as a function of two or more elementary kinds of information: the incidence rate and duration.

Incidence is the number of new cases arising in the population during a specified time period; duration is the average duration of the disease from onset to termination (recovery or death).

THE DEMENTIA SYNDROME

Boundaries

Table 1 sets out the criteria for the syndrome of dementia as set out by the American Psychiatric Association (1980) in its Diagnostic and Statistical Manual of the Mental Disorders (Third Edition)--the DSM-III. Each of the critieria under A to E must be fulfilled in order to reach the conclusion that a dementing syndrome is present. The left hand column is our interpretation (we rely here on Gurland and Toner, 1983. See also Small and Jarvik, 1982) of the essential features of DSM-3.

Loss of intellectual ability implies that it occurs after mature intelligence has been achieved (thus ruling out mental retardation which occurs from birth or early in childhood) and affects a broad range of cognitive functions (i.e. it is global rather than a specific defect such as language disturbance). In order to be sure that the intellectual impairment is abnormal and not one end of the normal range, it is important that the impairment is sufficient to account for a clear-cut disability in the performance of daily activities such as social or work tasks.

Category C in DSM-3 contains the least satisfactory of the criteria. Some of these may be difficult to recognize (e.g. impaired judgment, personality change); some may occur in other conditions (e.g. impaired thinking and semantics may occur in schizophrenia) or be difficult to recognize in those who are poorly educated. The aphasias and apraxias occur in various

TABLE 1. *Criteria for diagnosis of nonspecific dementia*

Essential features	Adapted from DSM III
Global cognitive impairment	A: Loss of intellectual ability with social and occupational dysfunction
Occurring after intellectual maturity	B: Memory impairment
Relevant disability chronologically related	C: One or more of: 1) Impaired thinking, semantics 2) Impaired judgement 3) Aphasias, apraxias, etc. 4) Personality change
Depression and acute confusional states ruled out	D: Consciousness not clouded
	E: Either: 1) Related organic cause; 2) Nonorganic mental disorders ruled out

localized lesions of the brain such as might occur in strokes or with tumors. These impairments are not especially helpful in making the diagnosis but can be identified as symptoms of dementia once the diagnosis is made.

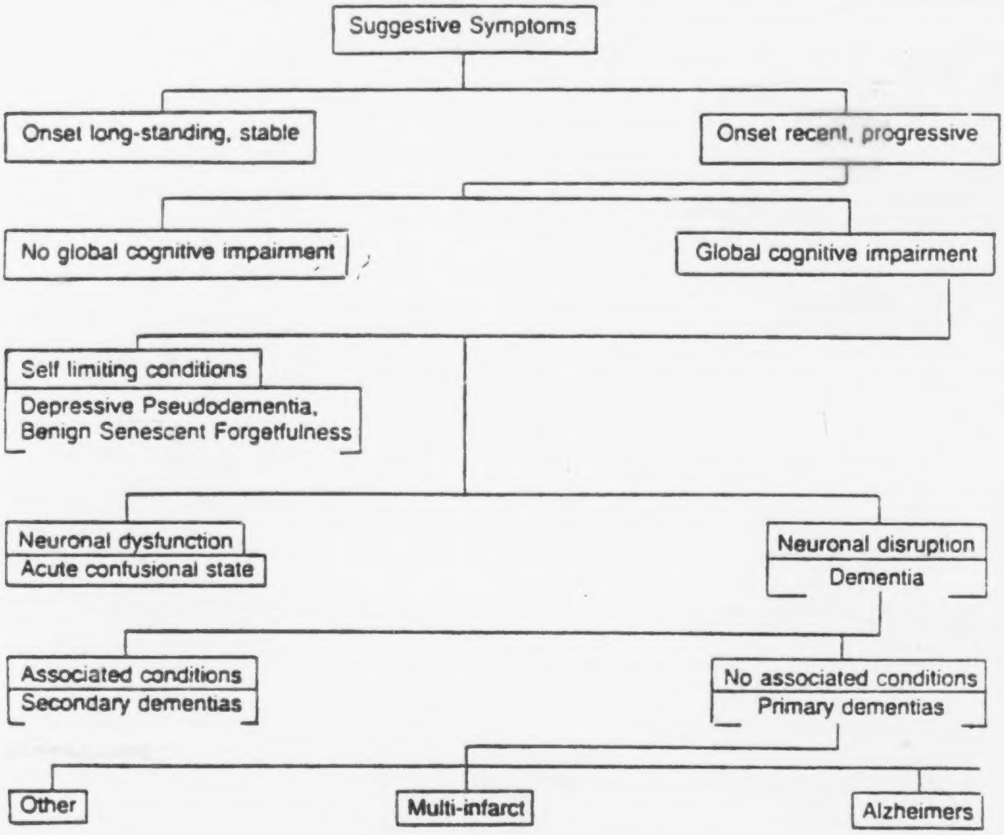
The criterion under D, that consciousness is not clouded (i.e that the person is alert and able to correctly perceive the external world and is not making supposed cognitive errors because they are delirious or stuperous), is aimed at excluding confusional states.

Subtypes of Dementia

The decision tree for diagnosis of dementia (Figure 1) presents a simplified scheme of how the clinical diagnosis occurs (for fuller expositions see Wells, 1977 or Roth, 1981) starting with a client who has symptoms suggestive of intellectual impairment. These symptoms include lapses of memory such as failing to recognize members of the family or close friends; disorientation such as not knowing the day, the date or the place, or as evidenced by wandering and getting lost; incompetence in carrying out the tasks of daily living (basic or instrumental activities of daily living) and consequent dependence on others; indiscrete behavior out of character for that person, disturbing behaviors such as aggression or screaming, or apathetic withdrawal.

In the face of such symptoms the first decision in the branching tree of diagnosis requires an assessment of when the

Figure 1. *Decision tree for diagnosis of dementia*


Suggestive Symptoms
Onset long-standing, stable
Onset recent, progressive
No global cognitive impairment
Global cognitive impairment
Self limiting conditions
Depressive Pseudodementia, Benign Senescent Forgetfulness
Neuronal dysfunction
Acute confusional state
Neuronal disruption
Dementia
Associated conditions
Secondary dementias
No associated conditions
Primary dementias
Other
Multi-infarct
Alzheimers

onset of the symptoms occurred and whether the course has been stable or progressive. If it has been lifelong and stable, then dementia can be excluded. If the onset is recent, that is at least within the last few years for early cases, and if evidence of progressive deterioration is present, the next decision is based on assessment of whether the intellectual impairment is widespread (global) or due to a specific neurological deficit. Tests of memory, orientation and new learning are useful to make this assessment. Specific neurological dysfunctions such as aphasia (speech impairment) and apraxia (not knowing how to use common objects) can occur in dementia, but memory, orientation and new learning are unimpaired when aphasia is the primary problem.

In the presence of global cognitive impairment, it is important to rule out depressive pseudo-dementia (instances in which a severe depression produces symptoms sometimes confused with those of dementia) and benign senescent forgetfulness (a non-serious if bothersome forgetfulness which does not seriously impair function or worsen dramatically over time (Kral, 1962). Both these conditions are usually self-limiting.

The next important decision is to identify conditions where no permanent damage has occurred to the brain although the neuronal circuits may be dysfunctional. These are the acute confusional states or deliria. The next step in the decision tree is to sort out the secondary from the primary dementias. Finally, the Alzheimer's, multi-infarct and other dementias are subclassififed.

Alzheimer's Disease is the most common and understanding of the mechanisms for this disorder (and thus the possibility of treatment) is undergoing fairly rapid development. Tissue changes in the brain can be recongized microscopically in that normally straight tubules within the nerve become tangled (neurofibrillary tangles) and the nerve endings become embedded in accumulations of broken down materials called senile plaques. These are not the only changes but they are very characteristic of Alheimer's disorder and are rarely found in other conditions in such concentrations. These distinctive neuropathological changes are of little practical help in diagnosis of living patients because brain biopsy (removal of living tissue) is only rarely justified or done.

These changes and the reduction in the number of nerve cells occur mostly in those regions of the brain that deal with memory and seem to involve mainly nerve cells that secrete a specific type of chemical (acetylcholine) which is one of the chemicals involved in transmitting messages from one nerve to another. Presumably this neurotransmitter system is intimately involved in the processes of memory.

The cause or causes of these changes are not presently known. In some cases there appears to be a genetic predisposition (Heston, 1981). However, there is no evidence yet that the disorder is strongly genetic in origin and we must assume that most cases are due to other causes. Toxicity due to certain metals, such as aluminum, is a possibility, but there is no strong evidence in favor of it. Certain types of dementia

(Creutzfeldt-Jakob Disease and Kuru) have been shown to be transmissable from one person to another but the mode of transmission is highly unusual and probably involves either ingesting tissue from a victim or transplantation. These types of dementia are not contagious in the usual sense and there is little evidence that Alzheimer's is transmissible under any circumstnces. Some alteration in the immune system, so that it attacks the body rather than germs and foreign particles, is another possibility that is being studied.

Alzheimer's disease may well be more than one condition or due to multiple causes (Seltzer and Stevenson, 1983; Jorm, 1985; Mayeux et al., 1985). However, we don't know yet how to distinguish these subtypes if they exist. Age is not regarded as a useful way of subtyping this condition. The previous distinction between a young type or presenile Alzheimer's dementia and an old type or senile dementia has been generally abandoned. There are some types of dementia, also involving tissue changes in the brain, which are quite different from Alheimer's disease. They are also uncommon. Pick's Disease is one and it tends to occur prior to age 65 and to show different brain changes. However, its most characeristic feature is that it is rare.

Multi-infarct Dementia is sometimes called arteriosclerotic dementia. Here a series of small strokes result in the death of limited areas of brain tissue any one of which might not cause intellectual impairment but which cumulatively lead to progressive dementia. Some of the same abnormalities that lead to a vulnerability to stroke are also predisposing to multi-infarct dementia: These are high blood pressure, high blood cholesterol, obesity, smoking, lack of exercise, and perhaps a genetic tendency. Possibly the same steps that can reduce hypertension and its effects on stroke and coronary artery disease might also reduce the chances of developing multi-infarct dementia. In theory, it should be possible to slow the course of the disorder and allow a certain amount of recovery by treating the underlying causes. Thus it may be important to distinguish this type of dementia from Alzheimer's Disease.

Features which suggest that a progressive dementia is multi-infarct rather than Alzheimer's Disease include: an abrupt onset, stepwise progression (deterioration occurs in sudden spurts with relatively stable intervals before the next exacerbation), emotional lability (the patient over reacts in responding to emotionally-laden topics), hypertension, stroke, evidence of arteriosclerosis elsewhere, signs of cardiovascular disease elsewhere in the body, focal neurological signs (evidence of limited neurological damage), fainting and fits.

Some of these symptoms have been included in a scale (Hachinkski et al., 1975) which is helpful in distinguishing multi-infarct from Alzheimer's type dementia. Alzheimer's Disease and multi-infarct dementia, both usually progressive in course and with no available treatment, constitute the large majority of the dementing disorders.

Other dementias, of which there are dozens each fairly rare in occurrence, here can be usefully thought of in three categories: progressive, static, and potentially reversible.

The progressive dementias (e.g. that associated with Parkinson's disease) have public health consequences likely quite similar to multi-infarct and Alzheimer dementia -- a course (whether steady or not) of progressive deterioration and ever greater dependence followed by premature death.

The static dementias (e.g. those due to head trauma) imply prolonged dependence with little change and no possibility of effective treatment.

Potentially reversible dementias include states which resemble dementia but are reversible (but may not produce the symptoms of acute confusional state, probably because they are of very slow onset). One of these conditions is normal-pressure hydrocephalus. In this condition there is an abnormality of the circulation of the cerebral spinal fluid which is normally secreted deep inside the brain and flows out of the brain through a system of canals and then around the surface of the brain until it is absorbed through vessels at the top of the brain and inside the skull. In rare instances, because of an abnormality of flow, the fluid accumulates and the brain is compressed. There is intellectual impairment, an alteration of the way the patient walks, and a tendency for urinary incontinence early on in the disorder. Brain imaging techniques assist in diagnosis and, in some cases, surgery can help provide a new avenue for the flow of fluid; sometimes the patient's intellectual performance improves a great deal.

Conditions such as this, which occur rarely, and the much more common conditions producing acute confusional states provide good reason for investigating thoroughly all new cases of dementia, of sudden deterioration in old cases of dementia.

EPIDEMIOLOGIC STUDIES

We have taken under review all studies undertaken since 1945 which have published detailed accounts of prevalence rates of dementing disorders in elderly populations. These studies and their key methodoogic features are shown in Table 2. This, (with some slight variations) is the body of work which published reviews and secondary analyses take into account. (Careful overviews of the European studies include Gunner-Svensson and Jensen, 1976; and Kay, 1977. The more recent reviews of Neugebauer (1980)and Mortimer and Hutton (1985) draw out the implications of these studies for prevalence and incidence in the United States).

Table 3 gives a crude view of the prevalence figures reported in these studies, ranging from 1% to nearly 8% in the non-U.S. studies and from over 2% to nearly 7% in the U.S. studies. Such great variation greatly limits the value of such studies in providing the key public health datum of prevalence (i.e. how many are there?) So we will devote some attention to gleaning from these studies improved best estimates of prevalence by trying to account for sources of variation in these reported prevalence rates other than possible real variation from study to study. Such other and "spurious" sources of variation, unfortunately, are many, while the number of studies is small.

Variations in the Population Studied

Table 2. Major Epidemiologic Surveys Yielding Prevalence Estimates for Dementing Conditions: Areas Studies, Type of Population Sampling, Ascertainment Methods and References

Investigator/Site/ Date of Study	Type of Area Studied	Type and Completeness of Population Sampling	Ascertainment Methods	References
Outside the United States				
Southern Sweden 1947	A rural district	Entire population over 18 years old. Less than 3% missing from survey.	Direct interview by psychiatrist; ~~where needed~~ reference to local informants, health records	Essen-Moller, 1956
Iceland 1957-72	Whole country	All 74-76 year olds	Medical records; psychiatric interviews	Helgason, 1973
Northern Scotland 1959-1960	A small town and surrounding	Entire population	GP with detailed personal knowledge and consultation with local health professionals	Primrose, 1962
Newcastle, England, 1960	Urban	Sample of the elderly from electoral rolls in a district of an industrial city	Psychiatric interview	Kay et al., 1964
Denmark, 1961	A rural island	All elderly	Researcher interview of ~~GPs~~ local MDs.	Nielson, 1962
England, 1961	Swansea	Only community residents	Interview	Parsons, 1965
Denmark, 1962	Small town in rural Denmark		Research interview of GP	Jensen, 1963

Investigator/Site Date of Study	Type of Area Studied	Type and Completeness of Population Sampling	Ascertainment Methods	References
Sweden, 1964	Rural	All 60+	Records and informants to obtain list of possible cases Psychiatric interview	Akesson, 1969
Copenhagen, Denmark, 1966-68	Suburbs	All 70 year olds 93% interviewed	Psychiatric interview	Bollerup, 1975
London, England 1975-76	London	Two-stage probability sample	Comprehensive semi-structured health and psychiatric interview	Gurland et al., 1983
Gottenburg, Sweden 1971-72	Small city	Sample of all 70 year olds. 86% given psychiatric exam	Psychiatric interview	Persson, 1980
Northern Scotland	Urban	Community residents 65+ 20-30% referrals		Broe et al, 1976
New Zealand	Gisborne	Random, age-stratified sample of all 65+ 5.1% refusals	1. Brief MSQ-type questionnaire if positive, then 2. Brief neuro-logical 3. History from informant 4. Blood tests	Campbell et al., 1983

24

Investigator/Site Date of Study	Type of Area Studied	Type and Completeness of Population Sampling	Ascertainment Methods	References
Finland, 1977-81	All of Finland	2-stage, age-stratified cluster sample of all over 30 years old (N=8,000) 97% interviewed 90% health examined	As part of health survey: those under 75 were screened 1. brief tests (Cattell's G-Factor and a verbal memory test - those positive and all those over 75 2. reviews of medical records - informant unknown	Sulkova et al.
Finland, 1976	City in SW Finland ~~Finland~~	All ages 1. All of hospital inpatients with suspected dementia had health records reviewed 2. all in geriatric nursing homes suspected of dementia were examined by neurologist 3. area health authority clients (getting home help and home nursing) and suspected of dementia were examined	- Clinical neurological exam - psychological tests	Molsa et al., 1982

Investigator/Site Date of Study	Type of Area Studied	Type and Completeness of Population Sampling	Ascertainment Methods	References
U.S. Studies				
Baltimore,	Urban			Pasamanick (1959, 1962)
Syracuse, 1952	Urban	All elderly residing in 6 census tracts		Gruenberg (1959)
New York City 1975-76	Urban	Two-stage probability sample	Comprehensive semi-structured health and psychiatric interview	Gurland et al., (1983)
Mississippi 1978	Copiah County	All individuals	1. Household interview to screen for dementia 2. All positive on screen given neurological exam	Schoenberg, 1985
the ECA studies				
New Haven 1980-81	Urban and	Multi-stage probability sample	Mini-mental state exam (MMSE) Score of 0-17	Robins, Holzer, Weissman, et al., 1984
St. Louis, 1981-82	Urban	Multi-stage probability sample	Mini-mental state exam (MMSE) Score of 0-17	Robins, Holzer, Weissman, et al., 1984
Baltimore, 1981-82	Urban	Multi-stage probability exam	Mini-mental state exam (MMSE) Score of 0-17	Robins, Holzer, Weissman, et al., 1984

Table 3 Major Epidemiologic Surveys Prevalence of Severe Dementias

Investigator(s)	Prevalance in Elderly Population		Notes
Outside the United States	N	Prevalence	
Essen-Moller, 1956	443	5.0%	age 60 and over
Primrose, 1962	222	4.5%	"Severe intellectual impairment"
Kay et al., 1964	443	5.7%	
Nielson, 1962	978	3.1%	
Akesson, 1969	2,071	.95%	age 60 and over
Parsons, 1965	228	4.4%	Community residents only
Jensen, 1963	546	1.1%	Community residents only
Bollerup, 1975	588	1.6%	70 year olds only
Broe, 1976	808	3.8%	Community residents only
Helgason, 1973	2,642	3.6%	74-76 year olds
Gurland et al., 1983	385	2.2%	Community residents only
Campbell et al., 1983	559	7.7%	
Sulkova et al.	1,880	6.7%	
Persson, 1980	392	1.3%	70 year olds only

Investigator(s)	Prevalance in Elderly Population		Notes
United States	N	Prevalence	
Pasamanick		4.0%	
Gruenberg		6.8%	"Psychosis of aging"
Gurland et al.	445	4.9%	Community residents only
Schoenberg et al.	4,503	2.2%	None of those over 60; 2.2% is prevalence for those 65+
New Haven ECA	607	5.0%	"Severe cognitive impairment"; community residents only
St. Louis ECA	576	5.1%	"Severe cognitive impairment"; community residents only
Baltimore ECA	923	4.0%	"Severe cognitive impairment"; community residents only

One possible major source of variation in the completeness of sampling the population is in the exclusion of those in institutions such as nursing homes, psychiatric hospitals, boarding houses and the like. Since such institutions can be (at present in the United States, usually are) major providers of care for the demented--taking care of a fifth to over a half of all those with a dementia, the inclusion of this portion of the population introduces a *certain and large* source of variation. The size of this variation is directly dependent on the proportion of all cases residing in such institutions and this proportion varies over time and from locale to locale and hence is impossible to adjust for in all the studies here considered. Hence we need to give special reliance on those studies which include *both* the community resident and the institutionalized population.

A further source of variation is in the age boundaries of the population selected. Most of the studies report (or allow calculation of) prevalence for all over 65 years old. A few studies report rates for all over 60 and this, given the much lower rates at 60-64), should result in lower rates reported by those studies of all over age 60. If we assumed the current U.S. age distribution for those over 60, a real 5% prevalence in the over 65+ and *no* cases in the 60-64 group then we find a 4% prevalence in the population over 60 and difference of 20%).

Another source of variation between studies might stem from differences in age structure but calculations show this to be trivial among the studies here considered. A few of the studies report rates for only a narrow age interval within the elderly population: 70 year olds (Bollerup, 1975; Persson, 1980), 74-76 year old (Helgason, 1973). For reasons already stated these are clearly not useful in estimating overall prevalence (though we do use them to describe age-specific prevalence, below.)

To lessen the variation in reported prevalence estimates due to differences in population definition, we need to place special value on studies of the entire elderly population 65 years of age and over. One consequence of this is that data on the U.S. population is severely limited.

The Epidemiuological Catchment Area (ECA) studies have not as yet published estimates for the entire population (which they did study) but only (as yet) for those outside of institutions, the one partial exception being the Esatern Baltimore ECA study which has published one account of prevalence for the elderly in nursing homes (German & Kramer, undated).

Gurland's study in New York City again reports on the community-resident population. Here a complementary study by the same research group of the elderly in institutions permits some more narrowly-bounded estimate of total prevalence.

Variations in Case-Funding

These studies may differ as well in the completeness of sampling and finding all individuals subject for study.

Many of the earlier European studies were conducted in small communities where the entire elderly population was easily, accurately and completely listed and where nearly all listed individuals cooperated in the study. This is a sharp contrast to the generally recent studies or studies of larger populations where a *sample* needs to be drawn of a population for which no list of individuals exists. Here typically a *sample* of geographical areas may be drawn, then a *sample* of households, then a sample of individuals in households is drawn, and some of these cooperate, others not.

Still where examined the biases introduced have not been shown to be other than trivial (Gurland, 1983; Holzer et al., 1985) though few studies devote any substantial attention to this possible source of bias.

Case Ascertainment Methods

These are perhaps the *largest* sources of variation in these studies. This is why the system of classification and steps in clinical diagnosis have been discussed in some detail earlier. Concluding that an individual suffers from a *dementing syndrome* requires a complex series of decisions (each fallible), calling upon detailed knowledge of the onset and course of symptoms, prior personality and adaptation, psychiatric status and history (Roth, 1981). Deciding what *kind* of dementia an individual has requires careful history taking, knowledge of medical details, and may require use of special medical and laboratory tests (see United States DHHS 1984 for recent recommendations of experts on information needed for accurate diagnosis) which (with a few exceptions) have not been undertaken in epidemiologic community studies.

The recent American studies, unfortunately, have been especially lacking here. Gruenberg's study in Syracuse ascertains only "psychosis of aging", a category which may include functional psychiatric disorders. The ECA studies report results (mostly) for a group of persons characterized as "cognitively impaired" and make no stronger claim, acknowledging that this may include persons suffering from "other mental conditions such as mental retardation, learning disability, a major depression" (Holzer, Tischler, Leaf, et al., 1984) and that cognitive impairment "does not make a diagnosis. Rather ... a need for further evaluation" (Folstein, Anthony, Parhad, et al., 1985).

Studies not vigorously working to include only those with dementing syndromes may then tend to overcount cases, i.e. include as cases some unknown proportion of those not demented.

Severity criteria may also exist. Akesson (1969) for instance, (precisely because he takes the criteria for dementia to be poorly defined), counts as cases only those who are "continuously disoriented" and reports the lowest prevalence of any study. Schoenberg et al. (1985) require their cases (among other criteria) to need "constant supervision" and evidence of "nocturnal disorientation."

Some of these studies include the category "mild dementia" and with extremely heterogeneous results. Nielson (1962) finds 5 cases of mild dementia for each case of severe dementia, Bollerup

(1975) finds 2, Essen-Moller 2, and Kay but 1. Henderson and Huppert (1984) have recently reviewed the problem of mild dementia and, while holding that mild dementia should be an area of particular research interest, conclude that there is little agreement about criteria for its presence and little knowledge of its natural history or course. The separation of those mild dementias which are an early stage of a progressive dementia from those which may follow a benign course is not yet possible. These basic problems are reflected in the great range of rates reported in epidemiological studies and indicate that even were the number of mild dementias of pressing import, only the most imprecise prevalence estimates could be forthcoming. We have not considered further these resuits. Current work (Berg et al., 1982, Storandt et al., 1984) attempts to specify and validate concepts of mild dementia and further studies may confirm this work and, at some future time, allow the epidemiology of the mild dementias to be better assessed.

Adjusting Rates for Total Prevalence

We have eliminated all studies not including both community and institution populations, studies covering only a narrow age segment, and the studies (Akesson and Schoenberg) with especially strict case ascertainment criteria. Where thought reaonable, adjustments for age boundaries of the population or to include those in institutions have been made. The resulting estimates (see Table 4) fall into the much narrower range of 4.5-6.7% for

Table 7 Adjusted Estimates of Total Prevalence of Dementia in the Elderly Population

Non-U.S. Studies	Original Published Estimate	Corrections	Improved Estimate
Essen-Moller, 1985	5.0	A	6.0%
Primrose	4.5	None	4.5%
Kay et al, 1984	5.7	None	5.7%
Gurland et al, 1983	2.2	B	4.7%
Sulkova et al	6.7	None	6.7%
			Med = 5.2%
U.S. Studies			
Gurland et al, 1983	4.9	B	7.4%
New Haven ECA	5.0	D	6.5%
St. Louis ECA	5.1	D	6.6%
Baltimore ~~ECA~~	4.0	D	5.5%
			Md = 6.5

Notes

A = Readjusted to 65+ population
B = Adusted to include institutionalized population studied by same investigators
D = Adjusted to include institutionalized population assuming 5% of elderly in institutions and 1/3 of these are demented.

the non-U.S. studies (median value of 5.2); for the U.S. studies these adjustments produce a range of estimates 5-7% with a median of 6.5%.

Occurrence of Dementia in the Non-elderly

Table 5 sets out the prevalence of all severe dementias in the non-elderly (less than 65 years of age usually). These range from 4 to 26 cases per 1000 population in the studies using diagnosis and with around 50 cases per 1000 identified in the ECA studies as cognitively impaired.

As a proportion of all cases of dementia, the non-elderly range from 0-11% in the diagnostic studies and suggesting that 5-10% as a reasonable range. The nmumber of cases in the elderly population would need to be increased 5-10% to estimate cases in the total poipulation (i.e. all age groups).

Sub-types of Dementia

Other Dementias

Table 6 sets out results from the few epidemiologic studies where some attempt has been made to sub-classify the types of dementias.

Taking first the prevalence of all types other than multi-infarct and Alzheimer's, reports range from 9% to 35% with six falling between 11% and 21%, a fairly narrow range considering that the studies range over many countries over a 20

Table 5. Major Epidemiologic Surveys. Prevalence of Dementia in the Non-Elderly

Investigator(s)	Prevalence in Non-senile (age<65)	Proportion of All Cases Who Are Not Elderly	Notes
Outside the United States			
Essen-Moller, 1956	.04% (1 case of 2107)	5%	18-59 vs 60
Primrose, 1962	(0-2 cases in 1400)	0%-20%	0-59 vs 60
Sulkova et al	.26% (16 in 6000)	11.0%	
Molsa et al.	.03% (39 in 150,000)	9.0%	
United States			
Schoenberg et al.	.045% (2 in 4422)		40-59 vs 60+
New Haven ECA	6%	33%	18-64 vs 65; Excludes those in institutions
St. Louis ECA	5%	31%	18-64 vs 65
Baltimore ECA	5%	22%	18-64 vs 65+

L

Table 6. Major Epidemiologic Surveys Sub-Types of Dementia

Investigator(s)	"Primary", "Alzheimer's"	"Multifarct", "Vascular", "Arteriosclerotic"	Other	Notes
Primrose, 1962	Senile psychosis = 60%	Psychosis with cerebral arteriosclerosis = 20% (2)	Other = 20% (2) Disseminated sclerosis blind loop syndrome with resulting malabsorption of B-group vitamins = 1	
Kay et al., 1964	31% ~~81%~~	50%	~~19%~~ 20%	
Bollerup, 1973	25% (8)	39% (12)	35% (11)	
Broe, 1976	71%	23%		
Gurland et al., 1983				
Sulkova	Primary = 50% (70)	Vascular = 39% (55)	Secondary = 11% (16) (posttraumatic encephalopathy (7); alcoholism (3); Parkinson's disease (2); alcoholism + respiratory failure, neurosyphilis, seguellae of encephalitis, MS (1);	

Investigator(s)	"Primary", "Alzheimer's"	"Multifarct", "Vascular", "Arteriosclerosis"	Other	Notes
Moisa	52% (218)	36% (152)	12% (Parkinson's (12); Trauma (12); Wernicke-Korsakoff (7); Lues (5); meningo-encephalitis (5); normal pressure hydrocephalus (3); intoxication (2); brain tumor, Huntington's chorea, anoxia + hypoxia (1)	
Gurland, et al.	"Alzheimer's" = 77% (12)	13% (3)	9% (2)	
Schoenberg, et al.	Primary, chronic progressive = 59%	Stroke (11) and stroke + alcoholism (1) = 16%	Chronic 18% progressive with uncertain etiology (12); rapid onset (2) unknown clinical course (6); meningitis, alcoholism, normal pressure hydrocephalus, encephalitis (1)	7.5% (6) unknown
Baltimore ECA	32%	46%	21%	65+ subjects only

year span. Further analysis of the sub-types themselves perhaps not warranted, given the very small number of cases in these studies.

Multi-infarct Dementias

Estimates for these (as a proportion of all dementias) range quite widely from 13% to 50%.

Alzheimer's

As we have pointed out earlier, this is a residual diagnosis: If a progressive dementia is identified occurring past middle-age and secondary causes are considered eliminated, the remaining diagnosis is Alzheimer's. Hence the rigor with which other purported causes of the dementia are excluded may greatly affect the proportion of dementias diagnosed as Alzheimer's. In the epidemiologic surveys the percent of all dementias diagnosed as Alzheimer's ranges very widely from 25% to 77%. The median around 50% is a convenient figure but there is no reason to believe that there is not real variation from study to study in these figures.

Is the Prevalence Rising?

Recent attention to the increased number of dementias include an "approaching epidemic" (Plum, 1979), a "quiet epidemic (British Medical Journal, 19__), part of a "rising pandemic" (Kramer, 1982,), or a "deluge" (Wells, 1981). The word epidemic has at least to the lay person dread connotations of something contagious, perhaps deadly (and indeed while not contagious the individual's chances of dementia given survival to the eighth decade are likely well over 20%). These statements are based really on three key facts: (1) the steeply rising prevalence of dementia with age (2) projected increases in the number of elderly in the U.S. population (though this is a general, not only a U.S., problem), (3) the increasing age of the elderly population.

The increase of prevalence of severe dementia during old age is seen in Figure 2, a fact about which there is no disagreement and about which estimates are within a surprisingly narrow range.

If we assume (*conservatively* and for ease of illustration) that prevalence is at 1% for those 65-74; 7% for those 75-85 and 25% for those 85+, we can apply these prevalence rates to the projected elderly population of the United States over the next 50 or 70 years. Figure 3 shows these projections with upper and lower bounds which assume possible substantial changes in prevalence (i.e. in incidence or duration). (See Table 7 for actual numbers). Given unchanged age-specific rates of prevalence, the total number of cases of elderly with dementia will increase fourfold by 2040. The overall prevalence rate with the total elderly population will increase by a half.

The contribution of various elderly age-groups to this increase is seen in Figure 4. The additional cases are largely from the 75+ group and especially from those 85 and over. The proportion of all elderly cases over the age of 85 would shift from perhaps 45% now to over 60%.

Figure 2. Age-Specific Prevalence Rates of Dementias Found in Various Studies

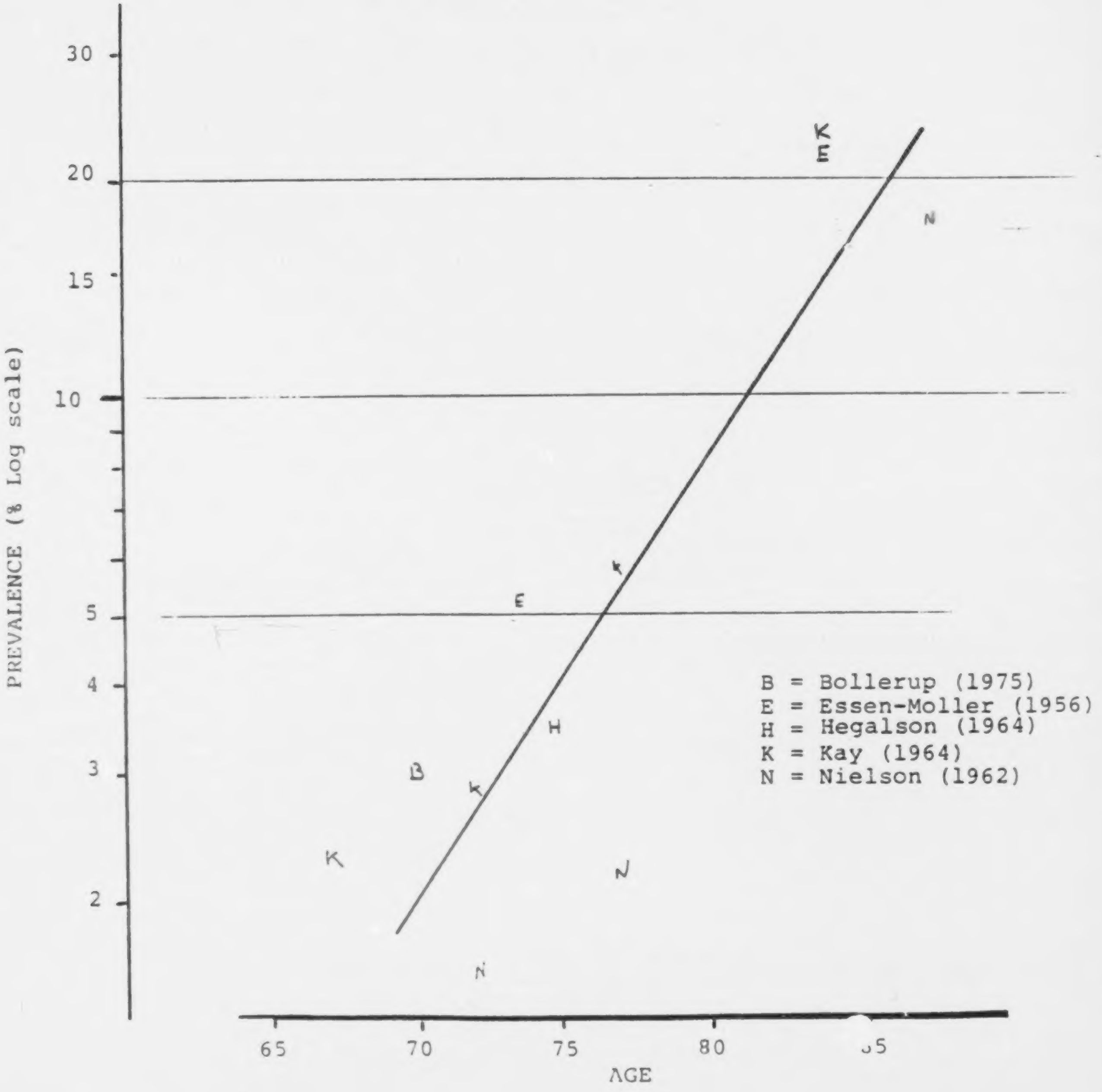


Figure 3. Projected Cases of Established Dementia in the United States

- Central estimate assumes constant age-specific prevalence
- Lower estimate assumes decrease of one half in duration or incidence
- Upper estimate assumes increase of one half in duration or incidence

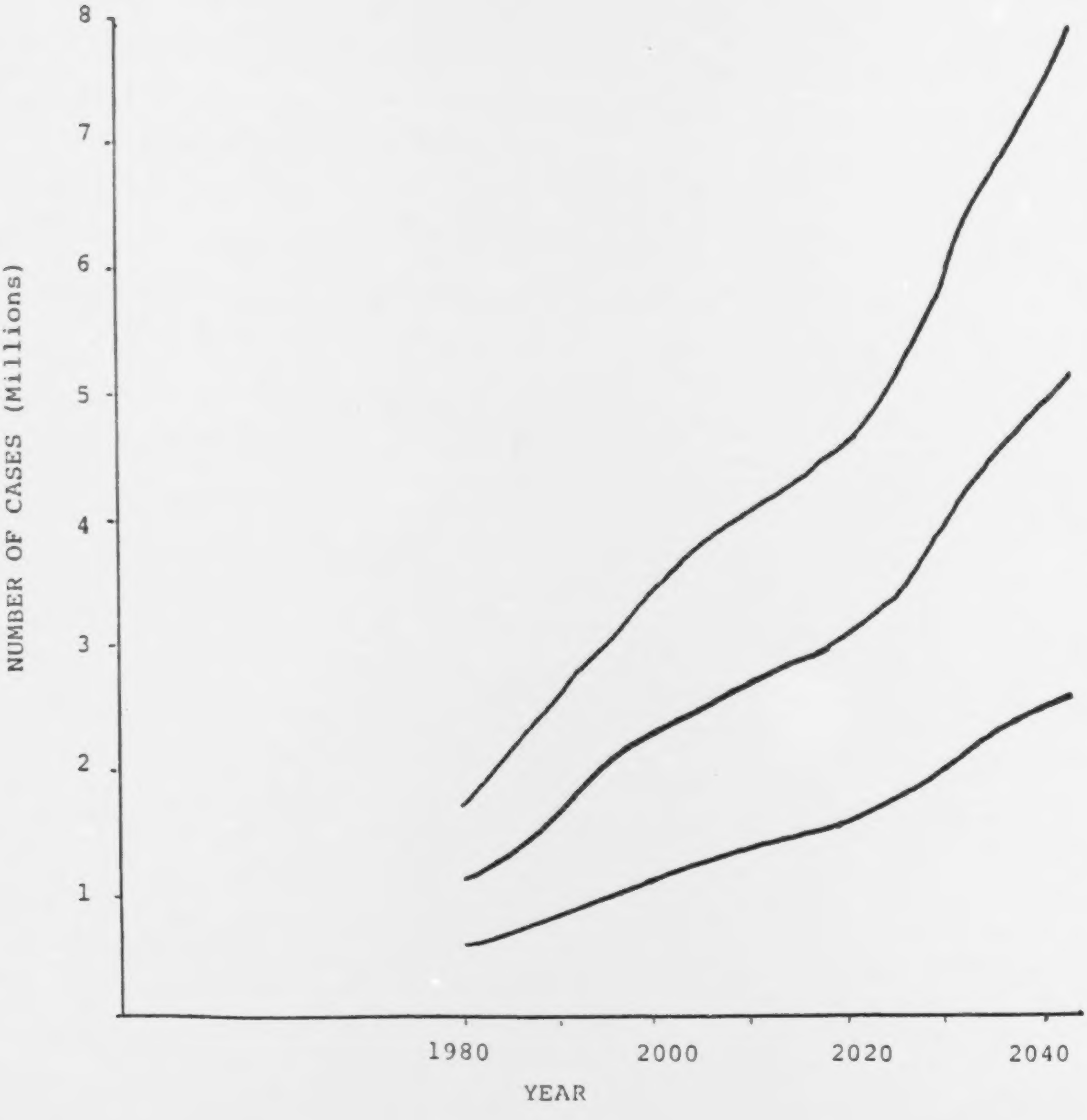


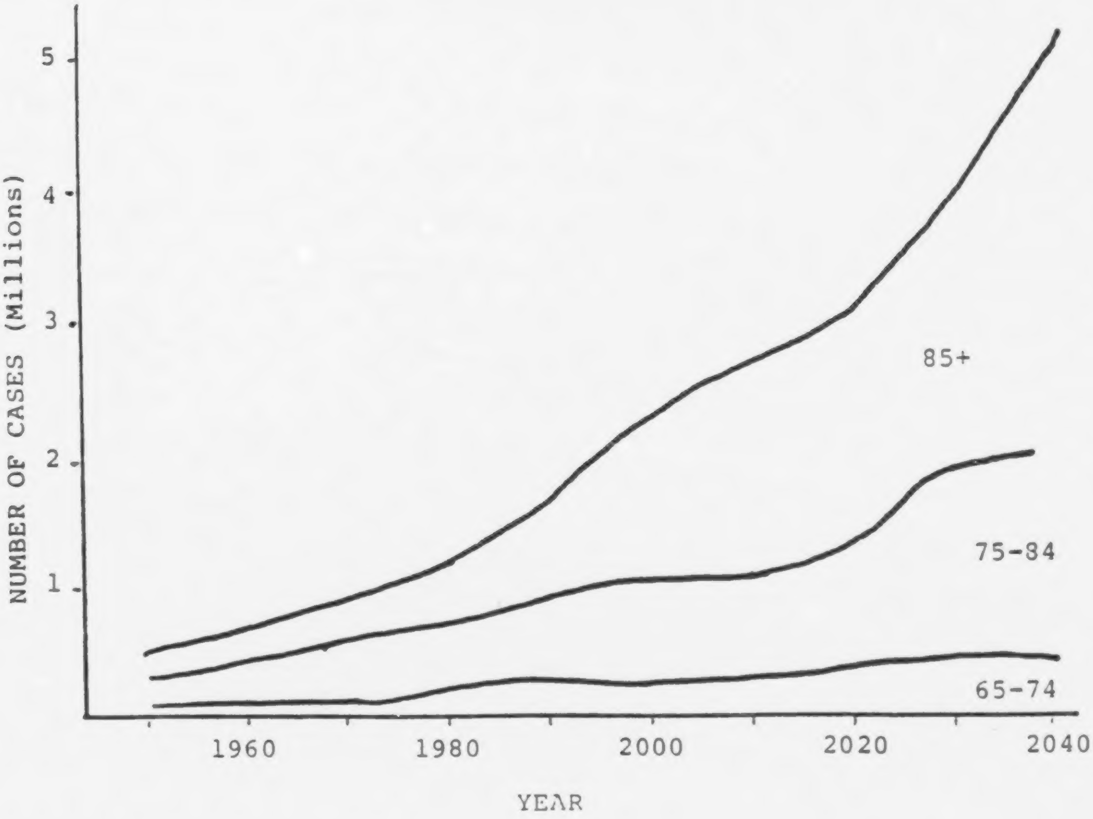
Table 7. U.S. Population Cases of Dementia, Prevalence of Dementia, and % of Cases in Older Age Groups

	1950	1960	1970	1980	1990	2000	2010	2020	2030	2040
A. U.S. Population (Millions)										
65-74	8.49	11.05	12.49	15.65	18.05	17.69	20.28	29.77	34.42	29.17
75-84	3.31	4.68	6.17	7.79	10.28	12.21	12.17	14.28	21.13	24.53
85+	.60	.90	1.43	2.27	3.46	5.14	6.82	7.34	8.80	12.95
TOTAL	12.4	16.7	20.1	25.7	31.8	35.0	39.3	51.4	64.3	66.6
B. Cases of Dementia (Thousands) Assuming Prevalence = 1% at ages 65-74; 7% at 75-84; 25% at 85+										
65-74	84.9	110.5	124.9	156.5	180.5	176.9	202.8	297.7	344.2	291.7
75-84	231.7	327.6	431.9	545.3	719.6	854.7	851.9	999.6	1,479.1	1,717.1
85+	150.0	225.0	357.5	567.5	865.0	1,285	1,705	1,835	2,200	3,234
TOTAL	466.6	663.1	914.3	1,269.3	1,765.1	2,316.6	2,759.7	3,132.3	4,023.3	5,242.8
C. Prevalence in 65+ Age Group (%)	3.76	3.97	4.55	4.94	5.55	6.62	7.02	6.10	6.26	7.87
D. % of All Cases Age 85+	32%	34%	39%	45%	49%	55%	62%	59%	55%	62%

Source of Population Estimates (1950-1080) and Projections (1990 on):

U.S. Census, Current Population Reports, Series P-23, No. 138
Demographic and Socioeconomic Aspects of Aging in the United States
U.S. Government Printing Office, Washington D.C., 1984.

Figure 4. Contribution of Elderly Age Groups to Projected Increase in Cases of Established Dementia



Is Incidence or Duration Changing?

Prevalence is a result of incidence (new cases arising per unit of time) and duration (how long the case persists in the case of *most* dementias duration is until death). If the age struture of the population is constant, then an overall incidence, for example of 1% per year together with a 5-year average duration, would result in a (5 + .01) 5% prevalence. Decomposing prevalence into incidence and duration would allow a more fine-grained approach to epidemiology but as we have seen, in the epidemiology of the dementias even reliable prevalence figures are quite few and only a handful of studies yield incidence rates--such studies require expensive monitoring of the population for new cases over-time (longitudinal studies are discussed extensively in Sluss, Gruenberg, and Kramer, 1981).

The Lundby study initiated by Essen-Moller in 1947 (and from which we have drawn prevalence data) was succeeded by a follow-up study of the same population by Hagnell (1966) ten years later and 25 years later by Hagnell and Ojisjo (Hagnell et al., 1981; Hagnell et al., 1983). A decreasing incidence was found between the two periods (1947-57 *vs* 1957-1972) such that the cumulative probability of having a severe dementia given survival to age 89 decreased from .37 to .26 for males and .45 to .30 for females. A later paper (Hagnell et al., 1983) showed this declining incidence to hold true for both multi-infarct and senile dementia. This single study is hardly enough to confirm a pattern of decline in incidence.

In any case, the declining incidence in the Lundby study was more than counterbalanced by increased survival of cases of dementia (perhaps due to improvement in medical care): the net result was increased prevalence (Gruenberg, 1978).

Svanborg (1984) reporting only changes in prevalence between sucessive cohorts of 70-year-olds in Goteborg, Sweden found no differences in prevalence of dementia between the two cohorts separated by 5 years. Reports on cases of dementia admitted to hospitals in Britain (Blessed and Wilson, 1981; Christie, 1982) pointed to increases in longevity over the past 20-40 years.

So the scanty evidence available is hardly conclusive in establishing increased prevalence of the dementias. But-- changes in age structure surely imply increased prevalence; possible decreases in the mortality associated with the dementias imply increased prevalence.

The Increasing Burden of Care

The implications of these projected increases in cases of dementia are still more dire when possible changes in the support and care for these dementias are considered.

Now the great burden of care falls to the "informal supports"--to umpaid, voluntary helpers almost always the spouse or children with, perhaps, three-quarters of all cases receiving no significant additional help from public programs (beyond those all elderly receive). The complement to these facts is seen in the fact that those in nursing homes are disproportionately those without available informal supports. One consequence of these facts is that small shifts in the pattern (e.g. availability, capacity, willingness) of informal supports may have great consequences for the formal supports.

Social and demographic changes are widely expected to weaken the systems of informal supports available to the elderly (Treas, 1977; Kobrin, 1976; U.S. Bureau of Census, 1984).

The great differences in life-span between males and females together with the fact that females typically marry men older than themselves result in a highly unbalanced sex ratio in old age. As recently as 1930, there was roughly a male for every female in the elderly population; today there are but .7 and this ratio will become slightly more skewed over the foreseeable future. For males, this means they are more likely to have a living spouse to care for them in event of need. However, for females--and especially for the quite elderly females most at risk for dementia--the chances of having a spouse to rely upon will grow somewhat smaller. Middle-aged married women now go to work -- in the past thirty years their participation in the labor force has risen from 11% ro over 45%. (U.S. Census, 1973). If it be imagined that females will leave the labor force when necessary to care for kin, recall that 30% of the mothers of pre-school children now work, leaving the care of their children to others. Surley an indication that they would as likely leave the care of aged parents to others (Treas, 1977). So these daughters will play a diminished role--there will be fewer of them and other commitments would more often preclude the often full-time responsibility of caring for a demented parent.

Figure 5. traces expected changes in the availability of children to care for the very aged (80+) through the year 2030. Over the years 1980 to 2000 we can expect even sharper increases than in the 1950-1980 period. The sharp dip (from the year 2000 to 2020) and consequent rise after 2020 reflect the "baby boom" of the 1940's and 1950's passing just through the 60-64 age interval and then the 80+ interval.

The broader facts of "societal dependency" are depicted in Figure 6. Here the entire elderly population is seen as a proportion of non-elderly adult: Here only slight increases will occur until the beginning of the baby boom generation reaches age 65 after the year 2010.

It seems only reasonable to expect that the burden of care for the demented--now borne largely by their families--may shift still further onto the shoulders of non-family members and become increasingly a public rather than a private burden.

It is difficult to foresee possible consequences of these changes since they will be in large part dependent upon future development (or lack of development) in formal provisions of services to the elderly and such formal provisions may (and have) undergone quite rapid changes in periods as short as a decade (Kramer, 1977). The widescale emptying of the elderly from public mental hospitals and the expansion of nursing homes are witness to the fact that patterns of public provision of services can change quite rapidly.

Figure 5. Familial Dependency Ratio (Population aged 80+ as a Proportion of those 60-64)

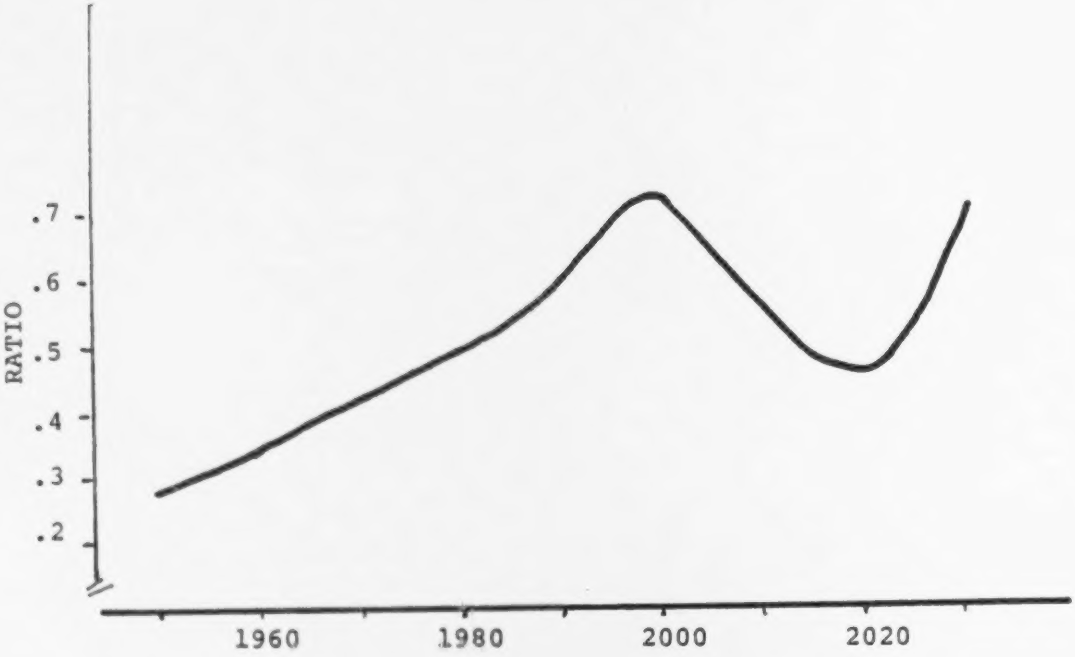
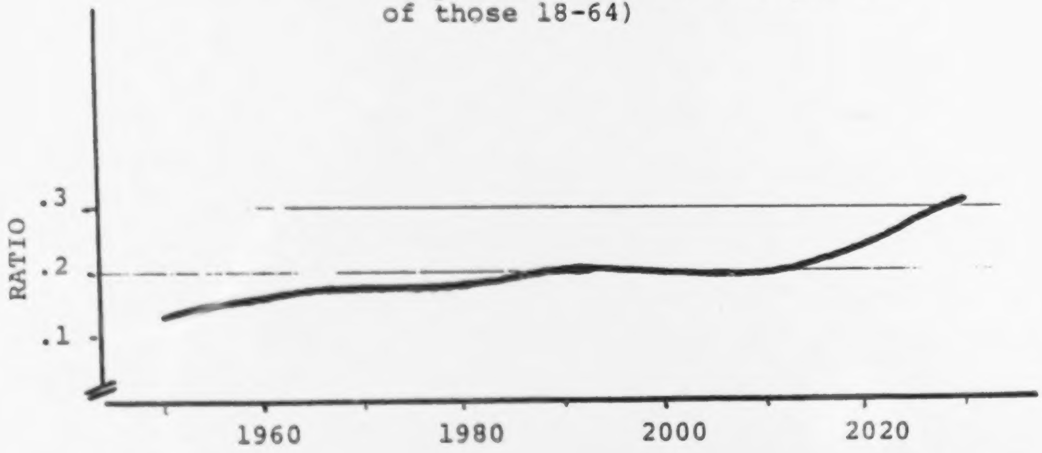


Figure 6. Societal Dependency Ratio (Population 65+ as a Proportion of those 18-64)



Source: U.S. Census, Current Population Reports, Series P-23, No.59. (Adapted from Table 6-10)

EPIDEMIOLOGIC RESEARCH

Recent Federally Supported Research

Recent federally-supported epidemiologic studies are listed in Appendix A. The most striking aspect of recent federal efforts is their paucity. For a disease which is a major public health problem--whether judged by its economic impact on the public purse, its involvement of millions as caretakers and supporters of the demented, or by the very subtantial chances of any individual of becoming demented in old age--epidemiologic work remains in a primitive state whether judged by the epidemiology of other disorders, by the history of distinguished European efforts or by state-of-the-art epidemiology as exemplified by the recent Finnish studies (Sulkova, 1985).

The ECA Studies

The single largest American effort in psychiatric epidemiology--the ECA studies--have not, at least in the epidemiology of dementia, produced any distinctive advance in this field and in many ways are a significant regress. These studies, fielded as the largest and most expensive epidemiologic studies of psychiatric disorder ever undertaken, used instruments for case ascertainment *never* tested in a community population.

The basic interview--the Diagnostic Interview Schedule--seems originally intended to judge symptoms of Dementia, their severity, frequency and distribution over time and eliminate possible alternative explanations and make a diagnosis of dementia (Robins, Holzer, Croughan et al. 1981). But in the end , a brief mental status exam was administered and all over an arbitrary error score as regarded "cognitively impaired"--a term which appears to be only another way of saying someone scored poorly on the test.

Two sites have yet to report results (due to later starting dates). Of the three sites reporting major results on the elderly, only one has reported data on the elderly in institutions and only one has rigorously attempted to comprehensively diagnose and evaluate by further study those identified as cognitively impaired.

The cooperative agreements (between NIMH and each study site) which supported these efforts now have been ended with the investigators at each site left free to apply (or not) for competitive research funds. Thus there is no assurance that cases of dementia located in the initial studies will be followed.

Recommended Studies

We are in a poor position to judge the competitive claims of epidemiologic studies of dementia as opposed to basic research, clinical research and health services research. The claims of epidemiology overlap with all those but it does have a distinctive role in informing public policy and decision-making.

Incidence/prevalence

In our view, little is to be gained by further studies where the main thrust is the only estimate of prevalence. Some suggestions (Gruenberg, 1978; Mortimer and Hutton, 1985) that incidence may decline after age 85 or 90 and have pointed out the possible implication of this finding (if true) in locating a group of individuals (those very old and unaffected) not subject to dementia and hence of special interest. Given the high incidence after age 85, small studies to either establish or refute this finding would be relatively straight-forward and inexpensive. Such studies might usefully be done as a part of Studies of the very old with dementias along a variety of lines. Health services research examining use of health services, and alternative service arrangements may be especially valuable since the very old (say, over 80 or 85) are very likely to be demented, very likely to lack strong informal supports, are increasing rapidly in number, and constitute an increasing proportion of all dementias.

Studies of Institutional Care

Perhaps half of all nursing home residents are demented and nursing home costs are a large portion of health care expenditures both for the public and for individuals for whom such expenditures are one of the most frequent sources of catastrophic health care expenditures (Congressional Budget Office, 197-).

Even basic descriptive nationwide surveys of such institutions are too infrequent. The last National Nursing Home Survey was evaluated in 1977-78 and the next in 1985-86 will not be reported for several years. Our understanding is that improvements in the survey to be undertaken will allow better identification of the elderly suffering from dementias but such studies should be more frequent, should include an admissions cohort to give a better view of short-term versus long-term care.

Adequacy of Current Ddementia Evaluations

Studies of referrals to special evaluation units seem to reveal that misdiagnosis of dementing syndrome is common, and that opportunities for effective medical treatment are missed. These treatment opportunities may exist *both* for those with progressive dementias who have overlooked and aggravating medical problems and for those with possible treatable reversible dementias.

How common such missed possibilities are remains, in our view, unknown. This number *may* be small but studies to investigate the adequacy of existing health care arrangements for the prompt and adequate identification of such problems should be undertaken, perhaps first in situations where poor provision might be expected: minorities, the poor, etc. Such studies could be usefully done, focussing perhaps on new admissions to nursing homes identified as demented and reviews of their recent medical diagnosis and treatment.

APPENDIX A:

Recent and Ongoing Federally-Funded Studies in the Epidemiology of the Dementias (DHHS, 1984)

National Institute on Aging

Barry Reisberg, M.D.
New York University, New York, N.Y.
Aging and Dementia: Longitudinal Course of Subgroups
R01 AG-03051-01

Dennis A. Evans, M.D.
Peter Bent Brigham Hospital, Boston, Mass.
Senile Dementia: Natural History
N01 AG-12106

Interagency agreement with
National Heart, Lung, and Blood Institute
Investigate Senile Dementia in Framingham Heart Study
Y02 AG-20040

Interagency agreement with
National Institute of Mental Health
Catchment Area Study of Senile Dementia
Y01 AG-90020

Leonard M. Schuman, M.D.
University of Minnesota and Minneapolis-St. Paul
Epidemiologic Study of Alzheimer's Disease
R01 AG-01529

National Institute of Mental Health

NIMH Epidemiologic Catchment Area Program

National Institute of Neurological and Communicative Disorders and Stroke

B. Schoenberg
OD/IRP/NINCDS
Epidemiology of Dementia
Z01 NS-02240-06

B. Schoenberg
OD/IRP/NINCDS
Racial Differentials in the Prevalence of Major Neurologic

Disorders and Surveys in Developing Countries
Z01 NS-02370-04

Veterans Administration

L.M. Schuman, M.D.
Miineapolis VAMC
Epidemiologic Study of Alzheimer's Disease

Administration on Aging

The following of the Long Term Care Gerontology Centers sponsored by the Administration on Aging (AOA) are engaged in activities relating to the epidemiology of the dementias:

Sidney Katz, M.D.
Southeastern New England Long-Term Care Gerontology Center
Brown University, Providence, R.I.
90-AT-2164

Barry J. Gurland, M.D.
Center for Geriatrics and Gerontology/Long Term Care
Columbia University, New York, N.Y.
90-AT-2155

Frederick Tavill, M.D.
Long Term Care Gerontology Center
Medical College of Wisconsin, Milwaukee, Wis.
90-AL-0010
1. Epidemiology

Maureen M. Henderson, M.D.
Pacific Northwest Long Term Care Center
University of Washington, Seattle, Wash.
90-AT-2152

REFERENCES

Adofson, R., Gottfries, C-G, Nystrom, L. et al., "Prevalence of Dementia Disorders in Institutionalized Swedish People," *Acta Psychiat. Scand.* 63:225-244, 1981.

Akesson, H.O., "A Population Study of Senile and Arteriosclerotic," *Human Heredity* 19:546-56, 1969.

Akhtar, A., Broe, G., Crombie, A. et al., "Disability and Dependence in the Elderly at Home," *Age and Aging* 2: 102-111, 1973.

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (Washington, D.C.: American Psychiatric Association, 1980).

Anthony, J.C., LeResche, L., Niam, V., et al., "Limits of the 'Mini-Mental State' as a Screening Test for Dementia and Delirium Among Hospital Patients," *Psychological Medicine* 12:397-408, 1982.

Barnes, R. & Raskind, M., "DSM-III Criteria and the Clinical Diagnosis of Dementia: A Nursing Home Study," *J. Geront*. 36(1):20-27, 1981.

Berg, L., Hughes, C. Cohen, L., et al., "Mild Senile Dementia of Alzheimer Type: Research Diagnostic Criteria, Recruitment and a Description of a Study Population," *J. Neurology, Neurosurgery and Psychiatry* 45:962-968, 1982.

Bergman, S., "The Social and Societal Impact of Senile Dementia" in *Senile Dementia: Outlook for the Future,* J. Werthheimer and M. Morris, eds. (New York: Alan R. Liss, 1985).

Bergmann, K., "Chronic Brain Failure-Epidemiological Aspects," *Age and Ageing* 6, Suppl.:4-8, 1977.

Bergmann, K., "Epidemiological Aspects of Dementia and Considerations in Planning Services," *Danish Medical Bulletin* Vol. 32 (Suppl 1):84-91, 1985.

Blazer, D., George, L.K., Landerman, R., et. al., "Psychiatric Disorders. A Rural/Urban Comparison," *Archives of General Psychiatry* 42:651-656, July 1985.

Blessed, G., Tomlinson, B.E. and Roth, M., "The Association Between Qualitative Measure of Dementia and Senile Change with Cerebral Matter of Elderly Subjects," *Brit. J. Psychiat.* 114:792-811, 1968.

Blessed, G. and Wilson, I.D., "The Contempory Natural History of Mental Disorder in Old Age," British J. Psychiat. 141:59-67, 1982.

Bollerup, T.R., "Prevalence of Mental Illness Among 70 Year Olds Domiciled in Nine Copenhagen Suburbs," Acta Psychiat. Scand. 51:327-339,1975.

Brody, J.A., "An Epidemiologist Views Senile Dementia - Facts and Fragments," American Journal of Epidemiology 115(2): 155-162, 1982.

Broe, G., Akhtar, A., Andrews, G., et al., "Neurological Disorder in the Elderly at Home," J. of Neurology, Neurosurgery and Psychiatry 39:362-366,1976.

Brunetti, P., "A Prevalence Survey of Mental Disorder in a Rural Commune in Vaucluse: Methodological Considerations."

Campbell, A., McCosh, L. Reinben, J. et. al., "Dementia in Old Age and the Need for Services," Age and Ageing 12: 11-16, 1983.

Christie, A., Train, J. "Change in Pattern of Care for the Demented," Brit. J. Psychiat. 144:9-15, 1984.

Cooper, B. and Bickel, H., "Population Screening and the Early Detection of Dementia Disorder in Old Age: A Review," Psychological Medicine 14:81-95, 1984.

Cross, P.S., Gurland, B.J., and Mann, A.H., "Long-Term Institutional Care of Demented Elderly People in New York City and London." Bulletin of the New York Academy of Medicine, 59,3:267-275. April 1983.

De Paulo, J.R. and Folstein, M.F., "Psychiatric Disturbances in Neurological Patients: Detection, Recognition, and Course," Annals of Neurology 4(3):225-228, 1978.

De Paulo, J., Folstein, M., Gordon, B., "Psychiatric Screening on a Neurological Ward," Psychological Medicine 10:125-132, 1980.

Eslinger, P., Damasio, A., Benton, A., et al. "Neuropsychologic Detection of Abnormal Mental Decline in Older Persons," JAMA 253(5):670-674, 1985.

Essen-Moller, E., "Individual Traits and Mobility in a Swedish Rural Population," Acta Psychiat. Scand. Suppl 100, 1956.

Fillenbaum, G., "Comparison of Two Brief Tests of Organic Brain Impairment, MSQ and the Short Portable MSQ," J.

American Geriatric Society 28(8):381-324, August 1980.

Finn, S. "Base Rates, Utilities, and DSM-III: Shortcomings of Fixed-Rate Systems of Psychodiagnosis" J. Abnormal Psychol. 91(4):294-302, 1982.

Folstein, M., Anthony, J.C. Parhad, I., et al. "The Meaning of Cognitive Impairment in the Elderly," J. American Geriatric Society 33(4):228-235, April 1985.

Folstein, M.F., Folstein, S.E., McHugh, P.R., "Mini-Mental State a Practical Method for Grading the Cognitive State Patients for the Clinician," J. Psychiatric Research 12: 189-198, 1975.

Folstein, M., and Lucas, M., "Implications of New Research for Care of Alzheimer's Disease," in Aging 2000: Our Health Care Destiny, C. Gaitz and T. Samorajshi, eds. (New York: Springer-Verlag, 1985).

Folstein, M., Romanoski, A., Nestadt, G. et al. NINCDS Final Report. Differential Diagnosis of Dementia in Eastern Baltimore. Mimeo, undated.

Freeman, F., "Evaluation of Patients with Progressive Intellectual Deterioration," Arch. Neurol. 33:658-659, 1976.

French, L. Schuman, L., Mortimer, J. et al., "A Case-control Study of Dementia of the Alzheimers Type," Amer. J. Epid. 121(3):414-421, 1985.

Garcia, C., Reding, M., Blass, J., "Overdiagnosis of Dementia," J. Amer. Geriatric Society 29(9):407-410, 1981.

German, P.S., Shapiro, S. & Skinner, E.A., "Mental Health of the Elderly: Use of Health and Mental Health Services," J. Amer. Geriatric Society 33(4):246-252, April 1985.

German, P. & Kramer, M., "Nursing Home Study of Eastern Baltimore Epidemiological Catchment Area Study" in M. Harper & B. Leibowitz (Eds.), Mental Illness in Nursing Homes: Agenda for Research (Washington D.C., N.I.M.H., undated pre-publication).

Goldman, R., The Social Impact of the Organic Dementias of the Aged," in Senile Dementia: A Biomedical Approach, K. Nanedy, ed. (New York: Elsevier North Holland, 1978).

Grove, W., Andreasen, N., McDonald-Scott, P. et al., "Reliability Studies of Psychiatric Diagnosis," Arch. General Psychiatry 38:408-413, 1981.

Gruenberg, E.M., "On the Frequency of Geriatric Psychoses By Age and Sex," *Interdiscipl. Topics Geront*. 3:45-45, 1969.

Gruenberg, E.M., "Epidemiology of Senile Dementia," in B.S. Schoenberg, ed,. *Advances in Neurology* (New York: Raven Press, 1978).

Gunner-Svensson, F. and Jensen, K., "Frequency of Mental Disorder in Old Aging," *Acta Psychiat. Scand.* 53: 283-297, 1976.

Gurland, B., "Public Health Aspects of Alzheimer's Disease and Related Dementias," in W. Kelly, ed., *Alzheimer's Disease and Related Dementias*, W. Kelly ed. (Springfield, Illinois: Charles C. Thomas, 1984).

Gurland, B. and Birkett, V.P., "The Senile and Pre-Senile Dementias," in M.H. Lader, ed. Handbook of Psychiatry 2. Mental Disorders and Somatic Illness (Cambridge, University of Cambridge, 1983, pp. 128-146).

Gurland, B. and Cross, P., "Public Health Perspectives on Alzheimer's Disease and Related Disorder and of Clinical Memory Testing," in L.W. Poon, ed., *The Handbook of Memory Assessment of Older Adults* (Washington, D.C.: American Psychological Association, In Press).

Gurland, B.J. and Cross, P.S., "Epidemiology of Psychopathology in Old Age," *Psychiatric Clinics of North America*, 5(1):11-26, April 1982.

Gurland, B., Cross, P., Defiguerido, J., et al., "A Cross-National Comparison of the Institutionalized Elderly in the Cities of New York and London." *Psychological Medicine 9*:781-788, 1979.

Gurland, B.J., Cross P., Mann, A. et al., "Comparisons of the Care of the Demented Elderly in New York and London," in J. Wertheimer and M. Marois (eds.) *Senile Dementia: Outlook for the Future* (New York: Alan R. Liss, Inc., pp. 327-337, 1984).

Gurland, B.J., Dean, L.L., Copeland, J., et al., " Criteria for the Diagnosis of Dementia in the Community Elderly," *The Gerontologist*, 22(2):180-185, 1982.

Gurland, B., Dean, L., Cross, P., et al., "The Epidemiology of Depression and Dementia in the Elderly. The Use of Multiple Indicaters of These Conditions," in J.O. Cole and J.E. Barrett, eds. *Psychopathalogy in the Aged*, (New York: Raven Press, 1980).

Gurland, B. and Toner, J., "Differentiating Dementia from

Nondementing Conditions," in R. Mayeux and W. Rogen eds., The Dementias (New York, Raven Press, 1983).

Hachenski, V.C., Ileff, L.D., Ziha, E., et al., "Cerebral Blood Flow in Dementia," Arch. Neurol. 32:632-637, Sept. 1975.

Hagnell, O., "Disease Expectancy and Incidence of Mental Illness Among the Aged," Acta Psychiat. Scand. Suppl.219:83-89.

Hagnell, O., Lanke, J., Rorsman, B., et al., "Does the Incidence of Age Psychosis Decrease," Neurobiology 7:201-211, 1981.

Hagnell, O., Lanke, J., Rorsman, B., et al., "Current Trends in the Incidence of Senile and Multi-Infarct Dementia," Archiv Fur Psychiatrie and Nervenkrankheiten 233: 423-438, 1983.

Helgason, "Epidemiology of Mental Disorder in Iceland", in Proceedings of the Fifth World Congress of Psychiatry, Mexico, 1971, R. De La Fuente and M. Weissman, Eds. (Amsterdam: Excerpta Medica Sect. VIIIB, 1973)

Helzer, J.E., Robins, L.N., McEroy, L.T., et al., "A Comparison of Clinical and Diagnostic Interview Schedule Diagnoses", Archives of General Psychiatry 42: 657-666, July 1983.

Henderson, A.S. and Huppert, F.A., [Editorial] "The Problem of Mild Dementia," Psychological Medicine 14:5-11, 1984.

Heston, C., Mastri, A., "The Genetics of Alzheimer's Disease," Archives of General Psychiatry 34:976-981, 1977.

Heston, L. and Mastri, A., "Age at Onset of Pick's and Alzheimer's Dementia: Inplications for Diagnosis and Research", Journal of Gerontology 37(4): 422-424, 1982.

Heston, L., Mastri, A., Anderson, E., et al., "Dementia of the Alzheimer Type. Clinical Genetics, Natural History, and Associated Conditions," Archives of General Psychiatry 38:1085-1090, 1981.

Heyman, A., Wilkinson, W.E., Stafford, J.A. et al., "Alzheimer's Disease: A Study of Epidemiological Aspects," Annals of Neurology 15(4):335-341, April 1984.

Holzer, C., Tishler, G., Leaf, P., et al., "An Epidemiologic Assessment of Cognitive Impairment in a Community Population," Research In Community and Mental Health 4:3-32, 1984.

Hughes, C.P., Berg, L., Danziger, W.L., Cohen, L.A. and Martin, R.L., "A New Clinical Scale for the Staging of Dementia," British Journal of Psychiatry 140:566-572, 1982.

Jacobs, J.W., Bernhard, M.N., Delgado, A., et al., "Screening for Organic Mental Syndromes in the Medically Ill," Annals of Internal Medicine 86:40-46, January 1977.

Jorm, A., "Subtypes of Alzheimer's Dementia: A Conceptual Analysis and Critical Review," Psychological Medicine 15:543-553, 1985.

Kahn, R.L., Goldfarb, A.I., Pollock, M., et al., "Brief Objective Measures for the Determination of Mental Status in the Aged," American Journal of Psychiatry 117(4): 326-328, October 1960.

Katzman, R. "The Prevalence and Malignancy of Alzheimer Disease, a Major Killer," (Editorial) Archives of Neurology 33:217-218, April 1976.

Katzman, R., Brown, T., Field, P., et al., "Validation of a Short Orientation-Memory-Concentration Test of Cognitive Impairment," American Journal of Psychiatry 140(6) 734-739, July 1983.

Katzman, R., and Karasu, T., "Differential Diagnosis of Dementia" In W.S. Fields (Ed.), Neurological and Sensory Disorders in the Elderly (New York, Stratton Intercontinental Medical Book Corp., 1975, pp. 103-132).

Kay, D.W.K., "Epidemiological Aspects of Organic Brain Disease in the Aged," in C.M. Gaitz (ed.) Aging and the Brain (New York, Plenum, 1972 pp. 15-27).

Kay, D.W.K., "The Epidemiology and Identification of Brain Deficit in the Elderly," in C. Eisdorer and R.O. Friedel (Eds.), Cognitive and Emotional Disturbance in the Elderly (Chicago, Year Book Medical Publishers, 1977, pp. 11-26).

Kay, D., Beamish, P. and Roth, M., "Old Age Mental Disorders in Newcastle upon Tyne. Part I: A Study of Prevalence," Brit. J. Psychiat. 110:146-158, 1964.

Kay, D., Bergmann, K., Foster, E., et al., "Mental Illness and Hospital Usage in the Elderly: A Random Sample Followed Up," Comprehensive Psychiatry 11(1):26-35, 1970.

Klein, L., Roca, R., McArthur, J., et al., "Diagnosing Dementia. Univariate and Multivariate Analyses of the

Mental States Examination," Journal of the American Geriatric Society 33(7):483-488, 1985.

Klerman, G., "Diagnosis of Psychiatric Disorder in Epidemiologic Field Studies," Archives of General Psychiatry 42:723-724, July 1985.

Kokmen, E., and Schoenberg, B.S., "Edpidemiological Patterns and Clinical Features of Dementia in a Defined U.S. Population," Annals of Neurology 8(1):116, 1980.

Kral, V.A., "Senescent Forgetfulness: Benign and Malignant," Canadian Medical Association Journal 86(6):257-260, 1962.

Kramer, M. "The Rising Pandemic of Mental Disorders and Associated Chronic Disease and Disabilities," Acta Psychiat. Scand. Suppl. 285:382-396, 1980.

Kramer, M., German, P.S., Anthony, J.C., et al., "Patterns of Mental Disorders Among the Elderly Residents of Eastern Baltimore," Journal of the American Geriatrics Society 33(4):236-245, April 1985.

Kobrin, F. "The Fall of Household Size and the Rise of the PRIMARY Individual in the United States" Demography 13:127-138, 1976.

Larson, E., Reifler, B., Featherstone, H., et al., "Dementia in Elderly Outpatients: A Prospective Study," Annals of Internal Medicine 100:417-423, 1984.

Larson, E., Reifler, B., Sumi, S., et al., "Diagnostic Evaluation of 200 Elderly Outpatients with Suspected Dementia," Journal of Gerontology 40(5):536-543, 1985.

Larsson, T., "Epidemiology and Genetics of Senile Dementia" in C. Muller and L. Ciompi (eds.), Senile Dementia (Bern: Hans Huber, 1968, pp.41-49).

Lauter, H. "What Do We Know About Alzheimer's Disease Today? An Overview," Danish Medical Bull. 32(1):1-21, 1985.

Lishman, W."Editorial Research Into The Dementias: Psychological Medicine 8: 353-356, 1978.

Liston, E., "The Clinical Phenomenology of Presenile Dementia," Journal of Nervous and Mental Disease 167(6):329-336, 1979.

Mace, N., "Long-Term Care of Patients with Dementia," A paper prepared for the Office of Technology Assessment. Mimeo, January 1985.

MacMahon, B. and Pugh, T. Epidemiology. Principles and Methods (Boston: Little, Brown, 1970).

Mayeux, R., Stern, Y., and Spanton, S. "Heterogeneity in Dementia of the Alzheimer Type: Evidence of Subgroups," Neurology 35:453-461, 1985.

McCartney, J.R., and Palmateer, L., "Assessment of Cognitive Deficit in Geriatric Patients," J. Amer. Geriat. Soc. 33(7):467-471, 1985.

McKhann, G., Drackman, D., Folstein, M. et al., "Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group Under the Auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease," Neurology 34:939-944, July 1984.

Meyer, N., "Diagnostic Distribution of Admissions to Impatient Services of State and County Mental Hospitals, United States, 1975. Mental Health Statistical Notes 138, U.S. National Institute of Mental Health, 1977.

Milazzo-Sayre, L., "Changes in the Age, Sex, and Diagnostic Composition of Resident Populations of State and County Mental Hospitals, United States, 1965-1973". Mental Health Statistical Note No. 146, U.S. National Institute of Mental Health, 1978.

Molsa, P., Marttila, R., and Rinne, U., "Epidemiology of Dementia in a Finnish Population," Acta. Neurol. Scand. 65: 541-552, 1982.

Molsa, P., Martilla, R., and Rinne, U., "Mortality of Patients with Dementia," Acta Neurol. Scand. Supp. 98, Vol. 69: 230-231.

Molsa, P., Paljarvi, L., and Rinne, U., et al., "Accuracy of Clinical Diagnosis in Dementia," Acta Neurol. Scand., Suppl. 98, Vol. 69: 232-233.

Mortimer, J., "Epidemiological Aspects of Alzheimer's Disease" in F. Pirozzolo & G. Maletta (eds.) The Aging Nervous System (New York, Praeger, 1980, pp. 307-332).

Mortimer, J., French, R., Hutton, J., et al., "Head Injury as a Risk Factor for Alzheimer's Disease," Neurology 35(2):264-267, 1985.

Mortimer, J., Hepburn, K., and Maletta, G., "Alzheimer's Disease: The Intersection of Diagnosis, Research and Long-Term Care," Bull. N.Y. Acad. Med. 61(4):331-343, 1985.

Mortimer, J., and Hutton, J., "Epidemiology and Etiology of Alzheimer's Disease" in J. Hutton & A. Kenny (eds.), Senile Dementia of the Alzheimer Type (New York, Alan R. Liss, Inc. In press).

Mortimer, J., Schumen, L. and French, L., "Epidemiology of Dementing Illness" in J. Mortimer & L. Schuman (eds.) The Epidemiology of Dementia (New York and Oxford: Oxford University Press, 1981, pp. 3-23).

Myers, J.K., Weissman, M.M., Tischler, G.L., et al., "Six-Month Prevalence of Psychiatric Disorder in Three Communities," Archives of General Psychiatry 41:959-967, October 1984.

Natelson, B.H., Haupt, E.J., Fleischer, E.J., et al., "Temporal Orientation and Education," Archives of Neurology 76:444-446, July 1979.

Neugebauer, R., "Formulation of Hypotheses About the True Precedence of Functional and Organic Psychiatric Disorder Among the Elderly in the United States," in B.P. Dohrenwend, D.S. Dohrenwend, M. Schwartz et al. (eds.) Mental Illness in the United States: Epidemiological Estimates (New York, Praeger, 1980, pp. 93-113).

Nielson, G., Robinson, G., "The Economics of Dementia," A Report to the Office of Technology Assessment. Mimeo, December 1984.

Nielson, J. "Geriatric-Psychiatric Investigations Within a Geographically Delimited Population Group," Acta Psychiatrica Scand. 39, Suppl. 196:203-205, 1963.

Nielson, J., Homma, A. and Bjorn-Henriksen T., "Follow-up 15 Years After a Geronto-Psychiatric Prevalence Study," J. Gerontology 32(5):554-561, 1977.

Nilsson, L.V. "Prevalence of Mental Disorders in a 70-Year-Old Urban Couple. A Cohort Comparison" J. Clinical Experimental Gerontology 5(2):101-120, 1983.

Nott, P., Fleminger, J., "Presenile Dementia: The Difficulties of Early Diagnosis," Acta Psychiat. Scand. 51:210-217, 1975.

Parsons, P.L., "Mental Health of Swansea's Old Folk," Brit. J. Prev. Svc. Med. 19:43-47, 1965.

Persson, G., "Prevalence of Mental Disorders in a 70-Year-Old Urban Population," Acta Psychiat. Scand. 62: 119-139, 1980.

Pfeffer, R.I., Kurosaki, T.T., and Harrah, C.H., "A Survey Diagnostic Tool for Senile Dementia," Amer. J. Epidemiology 114(4): 515-527, 1981.

Pfeiffer, E., "A Short Portable Mental Status Questionnaire for the Assessment of Organic Brain Deficit in Elderly Patients," J. American Geriatrics Society 22(10): 433-444, October 1975.

Plum, F., "Dementia: An Aproaching Epidemic," Nature 279:572-575, 31 May 1979.

Primrose, E.J.R., Psychological Illness. A Community Study (London: Tavistock Publications, 1962).

Reding, N., Haycox, J., Wigforss, K., et al., "Follow Up of Patients Referred to a Dementia Service," J. Amer. Geriat. Soc. 32(4):265-268, 1984.

Robins, L.N., "Epidemiology: Reflections on Testing the Validity of Psychiatric Interviews," Archives of General Psychiatry 42:918-924, September 1985.

Robins, L., Helyer, J., Croughen, J., et al., "National Institute of Mental Health Diagnostic Interview Schedule," Arch. Gen. Psychiat. 38:381-389, 1981.

Robins, L., Holzer, J., Weissman, M., et al., "Lifetime Prevalence of Specific Psychiatric Disorders in Three Sites," Arch. Gen. Psychiat. 41:949-958, 1984

Robins, P., Merchant, A., Nestadt, G., "Criteria for Diagnosing Reversible Dementia Caused by Depression: Validations by 2-Year Follow-up," Brit. J. Psychiat. 144:488-492, 1984.

Rosen, W., Terry, R., Field, P., et al., "Pathological Verification of Ischemic Care in Differentiation of Dementias," Annals of Neurology 7(5):486-488, 1980.

Ross, M., Toone, B., Garralda, M., et al., "Diagnostic Accuracy in Presenile Dementia", Brit. J. Psychiatry 134:161-168, 1979.

Roth, M., "The Diagnosis of Dementia in Late and Middle Life," in The Epidemiology of Dementia, J. Mortimer and L. Schuman (eds.) (New York: Oxford University Press, 1981).

Roth, M., "Some Strategies for Tackling the Problems of Senile Dementia and Related Disorders Within the Next Decade," Danish Medical Bulletin Vol. 32 (Suppl. 1): 82-

111, 1985.

Schoenberg, B.S., Anderson, D.W., and Haerer, A.F., "Severe Dementia, Prevalence and Clinical Features in a Biracial U.S. Population," Archives of Neurology 42:740-743, August 1985.

Seltzer, B., and Stevenson, I., "Organic Brain Syndromes: An Empirical Study and Critical Review," Am. J. Psychiat. 135:13:26, 1978.

Seltzer, B., and Stevenson, I., "A Comparison of Clinical Features of Early-and Late-Onset Primary Degenerative Dementia", Arch. Neurol. 40:143-146, 1983.

Shapiro, S., Skinner, E., Kessler, L., et al., "Utilization of Health and Mental Health Serivces", Archives of General Psychiatry 41: 971-978, 1984.

Shapiro, S., Skinner, E., Kramer, M., et al., "Measuring Need for Mental Health Servives in a General Population," Medical Care 23(9): 1033-1043, 1985.

Shepherd, M. "Editorial: Psychogeriatrics and the Neo-epidemiologists," Psychological Medicine 14:1-4, 1984.

Sluss, T., Greenberg, E., and Kramer, M. "The Use of Longitudinal Studies in the Investigation of Risk Factors for Senile Dementia - Alzheimer Type" in J. Mortimer & L. Schuman (Eds.) The Epidemiology of Dementia (New York, Oxford University Press, 1981 pp. 132-154).

Small, G., and Jarvik, L., "The Dementia Syndrome," Lancet 2:1443-1446, December 25, 1982.

Smyer, M.A., Hofland, B.F., and Jane, E.A., "Validity Study of the Short Portable Mental Status Questionnaire for the Elderly", J. Amer. Geriat. Soc. 27(6):263-269, June 1979.

Spitznagel, E.L. and Holzer, J.E., "A Proposed Solution to the Base Rate Problem in the Kappa Statistic," Archives of General Psychiatry 42:725-728, July 1985.

Storandt, M., Botwinick, J., Danziger, W.L., et al., "Psychometric Differentiation of Mild Senile Dementia of the Alzheimer Type," Archives of Neurology 41:497-499, May 1984.

Shrout, P., Spitzer, R. and Fleiss J. "Quantification of Agreement in Psychiatric Diagnosis Revisited.: Mimeo. Columbia University School of Public Health, Bureau of

Biostatistics, 1985.

Shrout, P.E. and Fleiss, J.E., "Reliability and Care Detection," in What Is a Case, J. Wing, P. Bebbington and L. Robins (Eds.) (London: Grant McIntyre, 1981).

Sulkava, R., Haltia, M., Paetau, A., et al., "Accuracy of Clinical Diagnosis in Primary Degenerative Dementia: Correlation with Neuropathological Findings," J. Neurology, Neurosurgery and Psychiatry 46:9-13, 1983.

Sulkava, R., Wikstrom, J., Aromaa, A., et al., "Prevalence of Severe Dementia in Finland," Neurology 35:1025-1029, July 1985.

Svanborg, A., Berg, S., Nelson, L., et al., "A Cohort Comparison of Functional Ability and Mental Disorders in Two Representative Samples of 70-Year-Olds" in J. Wertheimer and M. Marois, Senile Dementia: Outlook For the Future (New York, Alan R. Liss, 1984).

Terry, R.D. and Katzman, R., "Senile Dementia of the Alzheimer Type," Annals of Neurology 14(5):497-506, November 1985.

Tischler, G., Leaf, P., Holzer, C., et al., "Mental Health Care and the Elderly. I. Age, Psychiatric Status and Expressed Demand," Mimeo, 1985.

Tomlinson, B., "The Pathology of Dementia" in C. Wells (ed.) Dementia (2nd edition) (Philadelphia, F.A. Davis, 1977, pp. 113-153).

Treas, J., "Family Support Systems for the Aged. Some Social and Demographic Considerations," Gerontologist 17(6): 486-491, 1977.

United States Bureau of the Census. "Demographic and Socioeconomic Aspects of Aging in the United States" Current Population Reports, Series P-23, No. 138. Washington, D.C., U.S. Government Printing Office, 1984.

United States National Center for Health Services. The National Nursing Home Survey. Vital and Health Statistics: Series 13, No. 43. Washington, D.C. DHEW, 1979.

United States National Center for Health Statistics, "Changes in Mortality Among the Elderly: United States, 1940-1978," Vital and Health Statistics, Series 3, No. 22, DHHS Pub. No. (PHS) 82-1406, Washington, D.C., 1982.

United States National Center for Health Statistics, "Changing Mortality Patterns, Health Services, Utilization and Health Care Expenditures: United States, 1978-2003," Vital and Health Statistics, Series 3, No. 23. DHHS Pub. No. (PHS) 83-1407, Washington, D.C., 1983.

United States Department of Health and Human Services, Alzheimer's Disease. Report of the Secretary's Task Force on Alzheimer's Disease. (Washington, D.C.: U.S. Government Printing Office, 1984) DHHS Publication No. (ADM) 84-1323.

Wang, H.S., "Prognosis in Dementia and Related Disorders in the Aged," in R. Katzman, R.D. Terry and K.L. Bick (Eds.), Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7) (New York, Raven Press, 1978, pp. 309-313).

Wang, H.S., "Dementia of Old Age," in W.L. Smith and M. Kinsbourne (eds.) Aging and Dementia (New York, Spectrum, 1977, pp. 1-24).

Weisman, M.M., and Myers, J.K., Tischler, G.L., et al., "Psychiatric Disorders (DSM-III) and Cognitive Impairment Among the Edlerly in a U.S. Urban Community," Acta Psychiat. Scand. 71:366-379, 1985.

Wells, C. "Diagnostic Evaluation and Treatment in Dementia" in Dementia, C. Wells (ed.), Philadelphia: Davis, 1977.

Wells, C., "Role of Stroke in Dementia" [Editorial], Stroke 9(1):1-3, 1978.

Wells, C., "Chronic Brain Disease: An Overview," Amer. J. Psychiat. 135:1-12, 1978.

Wells, C., "A Deluge of Dementia" [Editorial], Psychosomatic 22(10)537-840, 1981.

Wilder, D., Teresi, J., Bennett, R. "Family Burden and Dementia," in The Dementias, R. Mayeux and W. Rosen, eds. (New York: Raven Press, 1983, pp. 239-263)

Withers E. And Hinton, J., "Three Forms of the Clinical Tests of the Sensorium and Their Reliability", Brit. J. Psychiat. 119:1-8, 1971.

Wittchen, H.V., Semler, G. and von Zerssen, D., "A Comparison of Two Diagnostic Methods," Arch. Gen. Psychiat. 42: 677-684, July 1985.

ACCURACY OF DIAGNOSIS AND CONSEQUENCES OF MISDIAGNOSIS OF DISORDERS CAUSING DEMENTIA

Robert Katzman, M. D.,

Bruce Lasker, M. D.,

and

Nancy Bernstein, M. A.

Department of Neurosciences,

School of Medicine,

University of California,

La Jolla, California 92023

[This contract report was originally written for and submitted to the Office of Technology Assessment, Washington, D. C., and was intended for use in the preparation of the OTA report Disorders Causing Dementia.]

June 1986

Acknowledgment

The authors gratefully acknowledge the contributions made by Robert W. Davignon during the preparation of this report. His skill and diligence shown during each stage of compiling, editing, and revising the text have been most helpful.

Table of Contents

ACCURACY OF DIAGNOSIS AND CONSEQUENCES OF MISDIAGNOSIS OF DISORDERS CAUSING DEMENTIA

I. DIAGNOSIS OF CLINICAL SYNDROME, DEMENTIA......................1

A. Historical Perspective..................................1

B. Current Distinctions....................................4

C. Summary--Dementia......................................22

II. ACCURACY OF DIFFERENTIAL DIAGNOSIS OF DEMENTING DISORDERS...24

A. Diseases that Present as Dementia......................24

B. Components of Diagnostic Workup........................26

C. Diagnostic Criteria....................................49

D. Diagnostic Errors: Current Status......................53

E. Summary--Differential Diagnosis........................56

III. PROGNOSIS AND PROGNOSTIC ACCURACY........................58

A. Estimates of Life Expectancy and Mortality.............58

B. Predictors of Mortality................................59

C. Functional Decline.....................................60

D. Predictors of Institutionalization.....................64

IV. PUBLIC HEALTH CONSEQUENCES OF MISDIAGNOSIS..................65

A. Misdiagnosis of Dementia Syndrome............................65

B. Misdiagnosis of Dementing Disorders..........................70

C. Impact on Families...73

D. Diagnostic Accuracy and Public Health Policy.................74

V. SUMMARY OF RECOMMENDATIONS...................................78

A. Physician Education Regarding Accepted Guidelines............78

B. Medicare Guidelines..78

C. Diagnostic Accuracy..78

D. Development of Specific Diagnostic Tests.....................78

E. Research Regarding Areas of Diagnostic Uncertainty...........78

List of Tables

Table 1. Disorders Presenting as Dementia

Table 2. Reversible Causes of Dementia

Table 3. Comparison of Diagnostic Criteria for Dementia

Table 4. Diagnosis of Dementia Syndrome: Misclassification Based on Follow-up Studies

Table 5. Disorders Producing Dementia: Diagnoses in Nine Clinical Series

Table 6. Pathological Diagnoses in Dementia

Table 7. Diagnostic Cerebral Biopsies

Table 8. Comparison of Diagnostic Criteria--Alzheimer's and "Primary Degenerative Dementia" (PDD)

ACCURACY OF DIAGNOSIS AND CONSEQUENCES OF MISDIAGNOSIS OF DISORDERS CAUSING DEMENTIA

I. DIAGNOSIS OF CLINICAL SYNDROME, DEMENTIA

This report addresses the issues of the medical and public health consequences of the misdiagnosis of dementia and of the disorders that produce dementia. It is critical in this regard to differentiate between the accuracy of diagnosis of the syndrome or symptom complex denoted by the term dementia and the accuracy of the diagnosis of the specific disorders that may present as dementia. It is now recognized that there are more than 70 such disorders, as shown in Tables 1 and 2. Alzheimer's disease is but 1 of these 70; its importance is that it alone accounts for more than half, perhaps nearer 60 percent, of all cases of dementia. Hence the accuracy of the diagnosis of Alzheimer's disease will be emphasized in this report.

A. Historical Perspective

1. Clinical and Mental Status: Changes Typical of Dementia

Interest in the accuracy of the diagnosis of dementia is a very recent phenomenon. During the first half of this century the chief medical concern about a dementing illness focused on neurosyphilis. After establishment of the serological test for syphilis, the discovery of arsenical therapy by Ehrlich, and the delineation of the late brain sequelae of this spirochetal infection and methods of treating it, physicians began to specialize in syphilology and a new medical specialty arose. But other dementing illnesses were often lumped together under rubrics such as senility ("she's getting old, what do you expect") or cerebral arteriosclerosis ("it's just hardening of the arteries, the pipes get rigid you know"). From a public health point of view it seemed to make little difference. Demented patients who could not be cared for at home could be sent to state mental hospitals or to community "chronic hospitals," without regard to the diagnosis. The numbers were not overwhelming and medical and community concern was at a minimum. The low level of medical interest was reflected in the available English language textbooks of neurology and psychiatry (there was a somewhat greater interest in the phenomenology of dementia by European psychiatrists), which gave little space to dementing illnesses.

Several events have radically changed this situation. Life expectancy, which was about 49 years at the turn of the century, will approach 79 years by the year 2000. Life expectancy of those over 60 has increased dramatically, thereby greatly increasing the number of individuals at risk for dementia. At the same time, the advent of potent neuroleptics and antidepressants for the treatment of schizophrenia and depression has made it possible to begin to treat such patients in the community. When economic considerations prompted many state governments to empty out state mental hospitals insofar as possible, most of the beds occupied by dementia patients were also closed. As more governmental funds were applied to medical care with the advent of Medicare and

Medicaid, state regulatory agencies instituted strict regulations and eligibility criteria resulting in the closing of many "chronic" hospitals. Thus patients with dementia, increasing in total numbers at a time of hospital closings, became an increasing burden on the community and on families.

2. Differentiation of Dementia from Other Syndromes

In the 1950s, intensive clinical studies of the elderly with cognitive and behavioral impairment by foresighted physicians, such as Martin Roth in Great Britain, led to the delineation of the clinical syndromes involved. The results of such studies made it possible to begin to diagnose the specific disorders producing these symptom complexes. In the 1960s breakthroughs in three specific disorders awakened medical interest in the diagnosis of dementia: 1) the discovery by Gajdusek and colleagues--a discovery important enough to have led to a Nobel Prize--of latent virus as the cause of Creutzfeldt-Jakob disease previously thought to be a degenerative disorder; 2) the studies by Terry and Kidd of the ultrastructural changes in the Alzheimer brain and the prospective quantitative study by Blessed, Tomlinson, and Roth relating the degree of Alzheimer pathology to the degree of dementia in the elderly, which formed the basis for the recognition of Alzheimer's as the most common form of dementia in the elderly; 3) and perhaps the most important of all from the diagnostic point of view, the delineation of "normal pressure hydrocephalus" by Adams and Hakim as a reversible cause of dementia. These advances were instrumental in focusing public attention upon the predominant form of dementia, Alzheimer's disease, and in creating recognition of the need for accurate differential diagnosis of the dementia syndrome in order to identify conditions that can be treated. A consensus statement on the importance of the diagnosis of reversible causes of dementia was developed by a work group sponsored by the National Institute on Aging (NIA; 1980) and criteria for the diagnosis of Alzheimer's were developed by a committee jointly sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984).

B. Current Distinctions

1. Definition of Dementia

"Dementia" is the term used to describe the symptom complex of intellectual deterioration in the adult. This symptom complex may be caused by more than 70 disorders but the most important of these is Alzheimer's disease, which alone accounts for more than half of the cases. The term "dementia" had been used by physicians for many decades but in 1952 the American Psychiatric Association in the first edition of its Diagnostic and Statistical Manual (DSM) did not include this term but instead introduced a new diagnostic term, "chronic organic brain syndrome" (Amer. Psych. Assoc. Task Force, 1952). The definition of the latter term included the requirement that the condition be progressive and irreversible. It becomes evident that many conditions that produced chronic symptoms of intellectual deterioration (for example, normal pressure hydrocephalus) were in fact reversible.

2. Advantages Based on Phenomenology and Clear Criteria

In 1980 the American Psychiatric Association dropped the invented label, chronic organic brain syndrome, and reintroduced "dementia," defined in terms of observable clinical criteria (Amer. Psych. Assoc. Task Force, 1980). The criteria were based upon clinical observation and judgement; no attempt was made to present specific operational criteria, such as scores on functional disability scales or mental status tests. Many clinicians who were not psychiatrists welcomed this approach and the DSM-III definition has been widely accepted.

3. Limitations

a. DSM-III. There are, however, limitations to the DSM-III diagnostic criteria. No definition exists of the degree of functional disability needed to qualify for the diagnosis of dementia and there is not as yet a consensus among workers in the field as to the appropriate scale to be used in these early cases. The definition stipulates impairment in memory and at least one other area of cognition. A small number of patients with dementing disorders have atypical presentations involving only a single area (e.g., language, visual perception, constructional ability, personality change, memory) for as long as 2 to 3 years, after which time more widespread involvement of cognitive functions becomes evident (Katzman, 1985; Mesulam, 1982; Crystal et al., 1982; Pogacar and Williams, 1984). Adherence to DSM-III criteria would unduly delay diagnosis in such patients. Another problem is the exclusion criteria which tend to be recursive in DSM-III. Thus the DSM-III criteria for dementia require exclusion of such conditions as depression but the criteria for depression in DSM-III require exclusion of dementia. The extent to which this problem with definition contributes to the frequent misdiagnosis of these two conditions has not been adequately explored. Finally, there is lack of agreement with the decision made in the formulation of DSM-III to separate the amnestic syndrome from dementia. The most common cause of the amnestic syndrome in the United States is Korsakoff's psychosis which is related to thiamine deficiency and alcoholism. Patients with this disorder are included by many workers in their dementia series. Despite these limitations, however, experience indicates that diagnostic accuracy has been significantly advanced by the DSM-III definition of dementia.

b. Comparison of DSM-III with Alternative Criteria for Diagnosis of Dementia. Although the DSM-III criteria for diagnosis of dementia have had wide impact, several alternative diagnostic criteria have been proposed. Table 3 provides a direct comparison of these criteria. Included in this table are the DSM-III criteria (Amer Pscyh. Assoc. Task Force, 1980), the ADRDA/NINCDS criteria (McKhann et al., 1984), the NIA/AMA criteria

(NIA, 1980), and the recently published modification of DSM-III by Jorm and Henderson (1985). All the 1980 and later definitions require evidence of loss of intellectual ability in a patient who is awake and alert; the ADRDA/NINCDS and the NIA/AMA definitions do not require specific evidence of deterioration in social or occupational function but the ADRDA/NINCDS stipulates that the intellectual dysfunction be demonstrable on a formal mental status test. Two of the sets of criteria require demonstration of memory impairment and impairment of another area of cognition; Jorm and Henderson will accept either or both in this regard and hence would make it possible to include the Korsakoff syndrome as a dementing disorder. Neither the ADRDA/NINCDS nor the NIA/AMA criteria require exclusion of other DSM-III diagnoses and therefore simplify the diagnosis of coincidental dementia and depression.

Comparison of the more recent sets of diagnostic criteria for dementia with the 1952 DSM-I criteria for "chronic organic brain syndrome," its designation for the dementia syndrome, reveals very important differences. The DSM-I criteria (Amer. Psych. Assoc. Task Force, 1952) required the presence of irreversibility and chronicity, two criteria eliminated from current diagnostic approaches. The question of reversibilty or irreversibility of dementia deserves comment. It has become evident that "irreversibility" is a term that may be appropriately applied to certain disorders but that its use reflects the state of ignorance of the medical profession at a given date; a condition that may be irreversible in the spring of 1986 might become reversible at a later time. There are many precedents. At the turn of the century, general paresis, the form of dementia that occurred in neurosyphilis, was indeed irreversible. In the early 1900s the discovery that fever therapy would reverse many of the symptoms of this disorder was considered important enough to result in a Nobel prize; and when specific antibiotics were discovered, the entity essentially disappeared. The same story can be told for the dementia associated with pernicious anemia; when an intrinsic factor was discovered the dementia suddenly moved from the category of irreversible to reversible; today with tests for blood levels of vitamin B-12 and with treatment with parenteral B-12 available, this disorder is among the most reversible.

Herpes simplex encephalitis, one of the most common of the viral encephalitides, was, only a few years ago, one of the most devastating; it is now treatable with antiviral agents if diagnosed promptly enough and the symptoms are often reversible. Other major examples of dementias which can be reversed if diagnosed early enough include the dementia associated with normal pressure hydrocephalus and with intracranial masses, such as subdural hematomas. As research progresses, it might be anticipated (or hoped) that presently irreversible conditions, such as Alzheimer's disease, will become reversible. Moreover, it is feasible to suppose that treatments will be discovered that might reverse symptoms of dementia before the underlying condition is treatable (an example is the effect of L-DOPA in reversing the motor symptoms of Parkinson's disease).

An important issue is the classification of confusional states associated with drug toxicity. In most instances such patients present acutely with some clouding of consciousness, and their condition is appropriately diagnosed as delirium. But at times an older individual may show the typical symptoms of dementia without any clouding of consciousness; moreover, the cognitive changes may come on insidiously and continue for months as use of an apparently innocuous medication continues. Although this scenario may occur with drugs with known anticholinergic properties, it is also seen as an idiosyncratic response to beta blockers used to treat hypertension, to digitalis-related medicines, or to diazepam-related sleep medicines. Elderly individuals sometimes do not metabolize drugs in the time course expected, and consequently blood concentrations build up over days or weeks and lead to chronic symptoms. A misdiagnosis of Alzheimer's disease may be made in individuals with such symptoms. Subsequent to the NIA/AMA task force on the reversible dementias, clinicians have been more aware of the possiblity that drug toxicity may cause the symptoms of dementia. They are now more likely to recommend a therapeutic trial consisting of symptomatic elimination or replacement of each medication that might be at fault. In addition, such a procedure will often reveal cases in which a medicine is not responsible by itself for the dementia symptoms, but has added to the cognitive impairment, an instance of a treatable "excess disability."

4. Problem Areas

a. Depression and Dementia. A most important diagnostic problem area is the differentiation of depression and dementia. The significance of the role of depression in the misdiagnosis of dementia was brought to the fore by the study of Ron et al. (1979). This study was of particular interest because it was carried out at Maudsley Hospital, the premiere psychiatric hospital in London. These investigators reported that on a 6-year follow up, 31 percent of the patients who had been diagnosed between 1963 and 1972 as having "presenile dementia" were in fact misdiagnosed and that the most common misdiagnosis occurred in patients who were depressed and had associated memory complaints. Subsequent series (Table 4) appeared to confirm the frequency of misdiagnosis.

The relationship of depression and dementia is a complex one. Individuals with typical manic-depressive disorders (bipolar affective disorder) or recurrent depressions (unipolar affective disorder) may, with aging, develop memory and other cognitive changes in association with their affective disorder. Folstein and McHugh (1978) reported that aggressive treatment of the depression (often with electroconvulsive therapy) in such patients resulted in improvement of cognition. These investigators found that a past history of depression, a subacute onset, and typical depressive vegetative signs and self-reports of depressed mood identified these patients. Rabins et al. (1984) have reported a 2-year follow-up of patients meeting these criteria showing continued improvement in memory and cognition, confirming the initial diagnosis of depression.

Depression presenting as dementia has been called "pseudodementia" by Kiloh (1961), a term that has been considered inappropriate by other authors (e.g., Reifler, 1982; Mahendra, 1983). Folstein and McHugh (1978) suggested that "dementia in depression" was a more appropriate term. Depression and dementia may coexist and in such patients treatment of depression may alleviate the affective symptoms without altering the dementing process (Reifler, 1982; Devanand and Nelson, 1985).

The relationship of dementia and depression may be even more complex. McCallister and Price (1982), Kral (1983), and Reding et al. (1985) have identified patients who initially met criteria for "pseudodementia" and later developed a frank dementia. There are several possible explanations. Perhaps dementia presents as depression in some patients, a conclusion endorsed by Reding et al. (1985). Or the diagnostic criteria for dementia used in their clinic were too strict--in favor of this possibility is the fact that a relatively insensitive mental status test, the Mental Status Questionnaire (MSQ), was in routine use. Or perhaps the biological bases of depression and dementia are entwined in a manner not presently understood. The apparently complex relationship of depression and dementia has been explored in a useful editorial by Mahendra (1985) who points out the "considerable challenge to his [the diagnostician's] prowess." Clearly we are faced with a limitation in our understanding of the relationships between these two conditions, a limitation that hinders our ability to make accurate diagnoses and may lead to significant errors in predictions.

b. Normal Age Changes and Dementia. The definition of the boundary between normal changes and dementia is the most difficult and perhaps insurmountable aspect of the diagnosis of dementia. On the one hand, changes in memory often accompany normal aging, an aspect which has been extensively studied by psychologists (see review by Katzman and Terry, 1983). On the other hand, the onset of certain of the dementias, particularly Alzheimer's disease, is very insidious. At the time of the first clinical examination, family members may disagree among themselves whether the first changes occurred 6 months or 3 years earlier. Kral (Kral and Muller, 1966; Kral, 1978) used the term "benign senescent forgetfulness" to describe individuals with memory changes who were still functional, but there is evidence that such memory changes are not always benign. In patients with mild cognitive changes one cannot make an exact diagnosis even with the very best neuropsychological tests available; only the likelihood of developing dementia can be estimated. In a prospective study of 488 volunteers, age 75 to 85 years, who were nondemented on initial examination, approximately 50 developed an unequivocal dementia over a 3-year period (R. Katzman et al., unpublished: "Bronx Aging Study"). Extensive neuropsychological tests had been carried out annually; the best predictor of dementia was the score on the Blessed mental status test. Subjects who initially made 0 to 2 errors (out of 33 possible errors) on this mental status examination developed dementia at a rate of less than 1 percent per year; those who made 5 to 8 errors developed dementia at a rate over 10 percent per year. But only one-third of those who made 5 to 8 errors have developed dementia as yet. The latter subset of subjects may be best described as an "at risk" group.

c. Dementia and Delirium. Delirium is a traditional medical term that was introduced as a diagnostic category by DSM-III. Delirium is a symptom complex used to describe global intellectual impairment associated with a clouded state of awareness. This syndrome was called "acute brain syndrome" in DMS-I. This phrase encompassed other terms, such as "acute confusional state," "toxic psychosis," and "metabolic encephalopathy." As indicated by these descriptions, delirium is often associated with metabolic or toxic conditions and most often is acute in onset and short in duration, but these features are not necessary criteria. Memory, orientation, and other cognitive areas are involved and mental status tests are abnormal, but the condition is differentiated from dementia on the basis of a fluctuating level of awareness. Delirium can accompany a high fever, pneumonia, cardiac failure, alcohol intake, alcohol withdrawal, high doses of psychoactive medications, and liver or kidney failure--in fact a wide spectrum of systemic, metabolic, or toxic disorders. Although focal intracranial processes, such as stroke, usually present with focal features (e.g., hemiparesis), such disorders may also be accompanied by delirium. Thus delirium often represents a medical emergency and is most often diagnosed in emergency rooms; the treatment of the delirium is the treatment of the causative condition. Therefore in most instances delirium is easily differentiated from dementia.

There are two instances in which a diagnostic problem may arise. Although delirium can occur in a person at any age if the metabolic insult is sufficiently great, it occurs more often in older patients and in patients with preexisting dementia, perhaps because there is less "cerebral reserve." If delirium due to an intercurrent infection occurs in a patient with an undiagnosed dementia, for example, there may be temporary diagnostic difficulty until the two conditions are sorted out. A second situation in which there is diagnostic difficulty occurs when the delirium is due to chronic exposure to a toxic source; for example, an older patient does not metabolize adequately a sleeping medication, the level of which then builds up, leading to a persistent daytime confusional state. In such situations delirium is not short lived if the patient takes the medication on a regular basis. In this particular instance it is not critical whether the label is delirium or dementia as long as the physician recognizes the cause and takes the patient off the precipitating medicine.

d. Validity of Diagnostic Series. When is the diagnosis of dementia to be considered correct? The difficulty in differentiating dementia and depression raises the question of what criteria for the validity of the diagnosis of dementia can be used. In the extensive literature on the diagnosis of dementia three implicit criteria have been employed. The first might be called the "authoritative opinion": a patient is referred to an academic center where an extensive examination is carried out and, often after a group discussion, a diagnosis is made. If this diagnosis differs from that of the referring or primary care physician, an error in the latter's diagnosis is assumed. Thus the initial series of Marsden and Harrison (1972), Garcia et al. (1984), and others are based upon a thorough, but one-time evaluation. The problem with this approach has been demonstrated by the work of Reding et al. (1984), described above, who found that half of the patients reported by Garcia et al. as examples of "pseudodementia" later developed frank dementia.

A second approach is to base diagnosis on a 1- to many-year follow-up. The majority of dementing illnesses progress. As a dementia progresses and cognitive loss becomes more evident, there is less uncertainty of diagnosis. If after several years cognitive impairment has not progressed or has improved, then the diagnosis of dementia can be questioned. This follow-up strategy was used, for example, by Reding et al. (1984, 1985), Lijtmaer et al. (1976), and others. Diagnosis by follow-up is clearly valid in terms of the question of whether dementia is or is not present when the cognitive state has clearly gotten significantly better or worse. However, this approach must be used cautiously in patients whose deficit has remained static, because a subset of Alzheimer patients have periods of 2 years or more during which their disease does not progress, a so-called plateau.

The greatest validity would be achieved if the clinical diagnoses were compared to predicted cerebral biopsy or autopsy diagnoses. Such comparisons are at present only available for a subset of dementia patients who have met research diagnostic criteria for Alzheimer's disease.

5. Tools/Technologies/Strategies to Improve Diagnosis of Dementia

The DSM-III diagnosis of dementia requires evidence of both cognitive and functional loss, although cognitive loss alone satisfies other criteria (see Table 3). Both forms of impairment may become readily apparent when the history is first taken. Intellectual changes involving several areas of cognition may be described, including repetitiousness, forgetting names and appointments, losing a chain of thought, difficulty in finding the right word, losing one's way, and losing objects. These symptoms are experienced occasionally by normal individuals but are exaggerated in dementia. Functional impairment may present as poor performance on the job or as difficulty in managing the household or withdrawal from hobbies or social activities; the most sensitive indicator of change in cognitive performance is often difficulty coping with fiscal affairs, such as the checkbook or tax form.

However, such symptoms may not be readily apparent early in the course of a dementia. Social conversation may be normal. The physician may not become aware of impairment during the usual course of history taking. However, impairment will become evident if specific probing of mental status is undertaken. Medical students are taught to do a mental status examination. This is reinforced during specialty training of neurologists, psychiatrists, and geriatricians. In practice many primary care physicians do not routinely carry out an adequate mental status examination and specialists may put it aside if another complaint appears dominant. For example, McCartney and Palmateer (1985) found that mental status examination had been carried out on only 4 of 165 patients over the age of 65 admitted to the general medical services of a major teaching hospital. As a consequence 50 patients with cognitive impairment were missed. Other instances of significant underdiagnosis of cognitive impairment have been found not only in general medical settings but also on neurology (Folstein et al., 1985), psychiatry (Hoffman, 1982), and rehabilitation services (Garcia et al., 1984), where such mistakes might not have been anticipated.

Thus the mental status examination remains the key to the diagnosis of dementia. The mental status examination as currently used was developed over decades of experience. Mayer-Gross (1931) and coworkers (Mayer-Gross and Guttmann, 1937) and other European psychiatrists were interested in identifying aspects of examination that distinguished generalized affections of the brain (that is, dementia and delirium) from local disorders (e.g., aphasias or language disorders produced by strokes or tumors localized to the temporal lobe of the dominant hemisphere). After Mayer-Gross migrated to Great Britain in the 1930s, several of his British students (Roth among them) began to formulate specific test items to formalize the mental status examination; a large number of individual items were subsequently examined in terms of their specificity (Shapiro et al., 1956) and following these studies items were combined to develop effective instruments. The two mental status tests now in widest use are the information-concentration-orientation test of Blessed et al. (1968) and the Mini-Mental State (MMS) examination of Folstein et al. (1975). The test of Blessed et al. is the most sensitive (two test items, the memory phrase and the months of the year backward, are harder than items on other tests) and therefore of greatest use in very early cases; it has the added advantage that it has been validated in two autopsy series, with the error score on the test correlating with a quantitative measure of pathology, that is the number of neuritic plaques per microscopic field in cases of Alzheimer's disease (Blessed et al., 1968; Katzman et al., 1983). The Blessed et al. test, however, is entirely verbal and measures recent and past memory, orientation, and concentration. The Mini-Mental State examination of Folstein et al. is broader in that it also tests language, writing, and drawing. These two tests have been brought together in a combined instrument that is being systematiccally tested. The Mental Status Questionnaire (Kahn et al., 1960) is contained within this combined test and can be scored separately. This combined test may be useful as a public health tool; it is, however, inappropriate to use this test with individuals who are mentally retarded or who have had a poor educational background. Also the tests are not appropriate for persons who are not fluent in English and for persons with different cultural backgrounds. Alternative tests need to be developed for such groups.

The use of other diagnostic tools in the differentiation of dementia and the differential diagnosis of dementia and depression has been suggested. Thus Ron et al. (1979) in their retrospective follow-up study found that both slowing on the EEG and neuropsychological test scores (the difference between WAIS verbal and performance scores) helped differentiate patients with presenile dementia from patients whose cognitive impairment was attributed to depression. The dexamethasone test has not been found useful in differentiating dementia and depression (Carnes et al., 1983; Balldin et al., 1983; McKeith, 1984; Katona and Aldridge, 1985).

Some physicians implicitly use the presence of atrophy on CT scan as a criterion of whether a patient is demented. Such use of CT is inappropriate. Dementia is a clinical syndrome that can be present in patients without atrophy on CT. Although cerebral atrophy is a common characteristic of Alzheimer's disease, some Alzheimer patients do not have evidence of atrophy on CT; conversely, many individuals during normal aging show a moderate degree of atrophy; consequently, the Alzheimer process and normal aging overlap in this regard, although group differences are real. However, in patients under age 60 significant atrophy on CT may be a useful indicator of a dementing process.

6. Misdiagnosis of Dementia

a. Diagnostic Errors in General Medical Settings. UNDERDIAGNOSIS of cognitive impairment occurs in general medical settings in situations where the cognitive impairment is not the presenting complaint. Cognitive impairment (both dementia and delirium) was found in more than one-fourth of the general medical inpatients at the Johns Hopkins Medical Institutions but had not been recognized by staff in a majority of these patients (Knights and Folstein, 1977); similar results were found on neurology service (DePaulo and Folstein, 1978) and in a rehabilitation hospital (Garcia et al., 1984) (Table 4). Underdiagnosis in these series occurs because of the failure by the physicians to carry out systematic mental status examinations.

b. Diagnostic Errors in Specialized Medical Settings. Underdiagnosis also occurs in the setting of specialized dementia clinics--Kral (1983) reported a 4- to 18-year follow-up of 22 patients with an initial diagnosis of pseudodementia. Twenty of these 22 patients had gone on to develop a progressive dementia of the Alzheimer's type. It might be argued that the diagnostic criteria (pre-DSM-III) initially used in this study were inadequate. Reding et al. (1985) reported similar results in a 2-year follow-up of a series of patients in whom diagnoses had been based on the DSM-III criteria. Thirty-one of the 225 subjects referred to their dementia clinic were initially diagnosed as having depression rather than dementia. On follow-up, however, 16 of the patients diagnosed as depressed and nondemented went on to develop frank dementia. The diagnoses in these 16 patients included Alzheimer-type dementia, multi-infarct state, Parkinson's disease, progressive supranuclear palsy, and spinocerebellar disorders.

In contrast, OVERDIAGNOSIS of dementia in patients referred to dementia clinics or referral practices has been reported to range from 10 to 50 percent (Garcia et al., 1981). An example is the report of Hoffman (1982) which indicates the diagnosis of dementia was changed in 40 percent of the patients admitted to a medical-psychiatric inpatient service and that in two-thirds of those with an altered diagnosis, a reversible condition was found. It is important, however, to note whether the report of misdiagnosis is based simply upon a single evaluation--no matter how complete--or upon follow-up since there is a significant error rate in the former group. It is also important to recognize that the nature of the patient referrals in these reports leads automatically to over- rather than underdiagnosis errors because the patient had been referred because of suspected dementia. Examples of overdiagnosis reported in series in which follow-up ascertainment has been used are shown in Table 4. It is striking that the rate of overdiagnosis has fallen dramatically in the two most recent series, both begun after DSM-III criteria became available.

C. Summary--Dementia

Dementia represents a symptom complex that may be caused by many disorders. Criteria for the diagnosis of this symptom complex have been well specified in the American Psychiatric Association's *Diagnostic and Statistical Manual*, third revision (1980). Failure to determine whether or not dementia is present is a greater source of misdiagnosis than are errors in the differential diagnoses of the individual conditions that produce dementia. Typically the presence of dementia is overlooked in patients who present in acute or chronic hospitals with other principal complaints because of the failure to carry out a systematic mental status examination. On the other hand, dementia is often overdiagnosed in older patients who complain of--or whose families complain of--beginning memory impairment. In a significant number of cases a treatable depression has been misdiagnosed as dementia under these circumstances. Although this situation has improved with the availability of DSM-III criteria for dementia and depression, serious problems remain in differentiating early dementia from depression in patients who show both mild cognitive impairments and depressive symptoms. Nor has the borderline between memory changes that occur in normal aging and beginning impairment in dementia been adequately defined. Very likely the latter boundary can only be established on a probability basis and a cohort of patients "at risk" for dementia identified.

II. ACCURACY OF DIFFERENTIAL DIAGNOSIS OF DEMENTING DISORDERS

A. Diseases that Present as Dementia

1. Clinical and Pathological Series

A number of published studies have reported the frequency of various disorders in patients presenting with the dementia syndrome. Several of these clinical series are summarized in Table 5; pathological series are in Table 6. Diagnoses on more than 700 clinical cases and 1100 pathological cases are presented in these tables. In both clinical and pathological series, Alzheimer's disease (or a synonymous diagnosis, such as degenerative dementia) accounts for over half of the cases. The clinical and pathological series diverge, however, in several aspects: clinical series report cases of toxic and metabolic dementias; these causes are not associated with diagnostic histological changes and hence are not included in the pathological series. Pathological series include a much higher percentage of vascular dementia than do most clinical series. This probably represents the sampling biases inherent in clinical series in which patients had been evaluated in a geriatric or dementia clinic or in a geriatric hospital. Thus patients who develop overt strokes may have been treated in an acute hospital and not sent to a dementia referral center. In support of this assumption is the fact that clinical studies based upon community sampling include a higher proportion of cases of vascular dementia (Folstein et al., 1985; R. Katzman et al., unpublished: "Bronx Aging Study").

Not all disorders that have been reported to present as dementia (Hasse, 1977; Katzman, 1984, 1986) appear in published series. This reflects both the relative infrequency of some of the disorders and the sampling bias that has occurred. Thus both factors may explain why dementia pugilistica (punch drunk syndrome) is not included in any of the published series. Series are gathered over years and therefore newly discovered entities--such as AIDS virus encephalopathy, which may become the third most common cause of dementia within the next 3 years--are not yet found in available series.

2. Age vs Frequency of Disorders that Produce Dementia

An important factor that must be taken into account in regard to the relative frequency of disorders that produce dementia is that of age. This factor will significantly impact the public health consequences of misdiagnosis. The incidence and prevalence of Alzheimer's disease increase exponentially with age at least to age 85. The incidence and prevalence of stroke also increase with age in an exponential fashion (Kurtzke, 1969; Katzman, 1983). In contrast, other disorders that produce dementia may be age-independent or peak during middle age (Table 6). Huntington's disease is one obvious example. An important reversible dementia that peaks in middle age is "normal pressure hydrocephalus" (perhaps better called "adult communicating hydrocephalus"). In a review, Katzman (1977) noted most reported cases were in individuals in their 50s and 60s. An autopsy series of dementia patients reported by Jellinger (1976) confirmed that the majority of hydrocephalus cases were under age 70, accounting for 5 percent of dementia cases under age 70 and only 0.3 percent of cases over the age of 70. But these "treatable" conditions do occur in persons whose first symptoms occur past the age of 75, as shown in the Bronx Aging Study (described above) in which one case of hydrocephalus and one of brain tumor (glioma) were among the first 35 cases of dementia to develop.

B. Components of Diagnostic Workup

1. Current Workup; Technical Limits; Risks, Benefits, Costs

a. Clinical Evaluation. The clinical evaluation--that is, the history, mental status, and physical and neurological examination--is central to the diagnosis of dementia and to the differential diagnosis of dementing illness. There is considerable variation as to how this clinical examination is carried out. Thus at one extreme, in a dementia clinic associated with a geriatric evaluation clinic and supported in part by a state grant, each patient is seen by an internist, neurologist, and psychiatrist; mental status tests and a neuropsychological battery are administered by a neuropsychologist; a nurse practitioner visits the home; a CT scan, blood tests, and other procedures needed are carried out; and a diagnosis is made at a consensus conference. At the other extreme, some patient families report that they have been told that their relative has Alzheimer's by a busy practitioner, based apparently upon a 10-minute examination and a CT scan. There is evidence that the first type of evaluation can result in a high level of accuracy in diagnosis, as shown by the autopsy follow-up of Larson et al. (1985) described below. The cost of such an evaluation in one specialized clinic which accepts Medicare reimbursement is $644 for the clinical and psychiatric evaluations and $718 for the laboratory tests, for a total of $1362.

It is important to point out the impact of current federal policy on the workup of a dementia patient. The combination of a complete history, physical and neurological examination with, for example, a mental status examination (at a minimum the combined Blessed and MMS), and a discussion of the problem with the family will take at least 1 hour and 15 minutes by a very experienced physician. Current Medicare reimbursement does not provide reimbursement for the additional time spent on a dementia patient, time that is almost certainly the most cost-effective part of the entire workup.

b. CT Scan. The CT scan is universally accepted as an essential component of the diagnostic workup. The CT scan is required for the diagnosis of hydrocephalus and mass lesions in the brain, including brain tumors and subdural hematomas. Dementia secondary to hydrocephalus and subdural hematoma can be arrested and sometimes reversed by prompt intervention; occasional benign brain tumors (e.g., pituitary adenomas, meningiomas) can be removed and symptoms arrested or reversed; other brain tumors, such as astrocytomas and microgliomas (primary brain reticulum cell sarcomas) may be usefully treated. Typical patterns of atrophy are sometimes diagnostic of Huntington's disease and Pick's disease. The CT scan of Biswanger's disease is also characteristic (Rosenberg et al., 1979). Although generalized cortical atrophy is not in itself diagnostic of Alzheimer's, the loss of tissue measured by combining cortical atrophy and ventricular enlargement is a useful adjunct in diagnosis (Gado et al., 1982). The cost of a noncontrast CT scan varies from about $225 to about $450 in different localities and with scanners of different resolution; in our estimates we use a figure of $341. The advantages of high-resolution scans include their capacity for identifying many vascular lesions, infarcts, and white matter changes that are missed on lower resolution scans.

c. Blood Tests--Systemic and Metabolic Disorders. Although systemic and metabolic disorders account for only 1 percent of patients presenting with symptoms of dementia, their identification is critical because progression of cognitive impairment can be arrested and sometimes function restored by treatment. Automated analytical systems make it possible to obtain 18 to 20 blood chemistries for less than $10, and a complete blood count adds only a few dollars. Unfortunately, tests of thyroid function, serum B-12 and follate levels, and syphilis are not included in available automated runs and their addition increases the cost to about $80. HTL-VIII antibody tests would increase the costs further. A modest federal effort to reward development of automation of these tests would be a cost-effective expenditure.

d. Chest X Ray and EKG. These are traditional parts of the routine annual examination and are included in most lists of workup for dementia. There are no studies justifying their cost effectiveness as part of the dementia workup, but information as to whether there is a tumor or infection in the lung or whether there has been a silent myocardial infarct is often useful. The cost for these two procedures varies; current Medicare reimbursement levels in California are $84 and $53 for chest X ray and EKG, respectively.

e. EEG. The electroencephalogram reflects the activity of the cerebral cortex and might be assumed to be a useful diagnostic tool. In patients with Alzheimer's and other forms of dementia, the typical 8- to 12-Herz occipital alpha rhythm may slow in frequency and disappear and the slower 4- to 7-Herz theta rhythm become predominant. Ron et al. (1979) found that the EEG did help discriminate between dementia and depression. The EEG is of specific use in a small subset of patients in whom cognitive impairment is the expression of seizure activity, particularly temporal lobe seizures, and in patients with Creutzfeldt-Jakob disease, who may develop a striking periodic rhythm. Although such patients constitute less than 1 percent of dementia patients, the condition is treatable and would justify the cost. The cost of an EEG varies from $100 to $160.

f. Neuropsychological Evaluation. The neuropsychological evaluation is not universally recommended as an essential part of the dementia workup and its cost effectiveness has not been determined. Many investigators, however, find neuropsychological testing to be very useful in confirming the presence of dementia and in identifying in a semiquantitative fashion the kinds of impaired function. It is valuable in distinguishing between dementia and depression (e.g., Ron et al., 1979) and between so-called cortical dementia (e.g., Alzheimer's) and subcortical dementias (e.g., progressive supranuclear palsy) (Cummings and Benson, 1984). Additionally, neuropsychological evaluation provides a precise way to follow changes in cognition. Neuropsychological evaluations often take a number of hours and hence are labor-intensive. Costs range up to $500. Medicare reimbursement, however, is limited to about $200.

The tests listed above constitute the core of the dementia workup. These tests are essentially risk-free; the small amount of X-ray exposure resulting from the CT and chest X ray will have little effect in the older patient being tested. Several other tests--described below--may be needed in special circumstances.

g. Lumbar Puncture. Lumbar puncture (LP) with analysis of the cerebrospinal fluid (CSF) has been traditionally included in the routine dementia workup and is needed to diagnose such treatable causes of dementia as neurosyphilis and chronic fungal meningitis. Infectious etiologies of dementia, however, have been found to be uncommon. In a retrospective study of the results of lumbar puncture in 402 patients, hospitalized in two major teaching hospitals for the evaluation of dementia, 4 patients with central nervous system infections were found, 2 with fungus infections (due to Cryptococcus), 1 with tuberculosis, and 1 with Staphylococcus infection (Becker et al., 1985). In all these patients there was a subacute onset of a change in mental status and all had either fever or signs of meningeal irritation (that is, a stiff neck). The authors concluded that in the absence of such signs, "LP and CSF analysis should not be part of the routine evaluation of patients with dementia." A new category of patients in whom LP is needed are those with cognitive changes who have AIDS, because the dementia in AIDS can be due either to coincident opportunistic infections or to primary AIDS virus infection; the presence of the virus can now be demonstrated in CSF. The risk of an LP includes that of the post-LP headache which, however, is less frequent in older patients. Post-LP infection is a theoretical risk but is not seen in routine practice. The cost of CSF analysis is about $70.

h. Tests of CSF Circulation. In patients in whom the CT scan suggests the presence of hydrocephalus, special procedures, such as isotope cisternography or infusion test, may be necessary before surgical shunting.

In patients with suspected vascular dementia a search for etiologies, such as carotid artery or cardiac sources of embolization, is often carried out. Although this is accepted and rational practice, its diagnostic value has not been adequately studied (see, for example, Postiglione et al., 1985).

There are several tests which measure functions that are altered in dementia but which are not diagnostic; these tests can be considered to be of research interest but have no proven value in the clinical diagnosis of dementia. These include measurements of cerebral blood flow with the xenon inhalation technique and measurements of evoked potentials.

2. Cerebral Biopsy

At the present time, and in the absence of specific biochemical markers, the definitive diagnosis of Alzheimer's disease, Pick's disease, and Creutzfeldt-Jakob disease depends upon confirmation by microscopic examination of the presence of characteristic changes in neurons of the cerebral cortex--in the case of Alzheimer's disease, the presence of abnormal foci of degenerating nerve endings, termed a neuritic plaque, and the presence of neurofibrillary tangles, abnormal nerve cells containing accumulations of submicroscopic fibrils; in the case of Pick's disease, abnormal inclusions in neurons, termed Pick bodies; in the case of Creutzfeldt-Jakob disease, by the spongy appearance of the cortex resulting from a particular pattern of nerve cell drop out and gliosis. Thus, during life one can only achieve a definitive diagnosis for these conditions by the use of cerebral biopsy, that is, by the surgical removal of a small piece of cerebral cortex with subsequent histological examination supplemented by electron microscopic examination and by biochemical and virological studies. In addition to its critical role in diagnosis, cerebral biospy has played a central role in advancing the understanding of these diseases. The classical electron microscopic studies of Alzheimer's by Terry (1963; Terry et al., 1964) and Kidd (1964) depended upon the availability of brain biopsy; the recent studies of Bowen et al. (1982) demonstrating the involvement of the cholinergic system during the first year of symptoms in Alzheimer's disease depended upon the availability of biopsy specimens; the demonstration that Creutzfeldt-Jakob disease is transmissable to chimpanzees primarily, but not exclusively, involved implantation of biopsy specimens into chimpanzee brain. Yet the cerebral biopsy procedure is used in much fewer than 1 percent of dementia patients in the United States, although it is used more commonly in Great Britain. Is this conservative approach justified by the risks of biopsy? How frequently do biopsies give unequivocal answers?

There are two surgical approaches to brain biopsy: 1) open surgery with removal of a piece of cerebral cortex under direct visualization; if the presentation is that of a diffuse disease, the biopsy is carried out in the right frontal lobe (in right-handed patients) as there is no apparent neurological defect that results from removal of a small amount of cortex in this "silent" area; 2) needle biopsy under stereotaxic or CT guidance. In the first procedure about a cubic centimeter block of tissue is removed; in the second a small core of tissue the diameter of a needle is removed. In practice, the first procedure is used when disease of the cerebral cortex, such as the dementias, is present because this procedure preserves the architecture of the cortex which may be important in diagnosis; in addition, the gram of tissue usually removed makes it possible to carry out special staining procedures needed for diagnosis of dementias and illnesses (such as silver or thioflavine stains for neurofibrillary tangles); also this amount of tissue permits biochemical analysis (for example, for markers of the cholinergic system) and immunohistochemistry to be carried out, thus increasing the chance of specific diagnosis. In practice, the second procedure is used if a lesion is deep to the cortex, particularly if it is a suspected tumor or inflammatory lesion. Needle biopsies have been used extensively to confirm the diagnosis of herpes encephalitis which affects the medial temporal region. This is the only condition which regularly presents with mental status changes in which needle biopsy is performed.

Needle biopsies were seldom carried out for diagnostic purposes in subjects with symptoms of diffuse cerebral disease prior to the availability of antibiotics. Cerebral biopsy, however, came into use, particularly in Europe, in the late 1950s and early 1960s. We have been able to identify 10 series (Table 7) with diagnostic and/or risk data encompassing 551 patients.

A majority of the patients reported were children in whom diagnoses of recessive metabolic disorder (such as Tay-Sachs disease) was sought. Because most of the recessive metabolic disorders can now be diagnosed using skin cultures or other peripheral tissues, such biopsies are not so common today. There are 4 series which focus on adult patients with symptoms of dementia and include 132 cases.

a. Diagnostic Accuracy. In the five general series (encompassing 419 patients, predominantly children), cerebral biopsy yielded a specific diagnosis in 40.0 percent; 34.5 percent of the biopsies were abnormal but not diagnostic, and 25.5 percent were normal (Antunes, 1963; Blackwood and Cumings, 1966; Eadie, 1964; Groves and Møller, 1966; all summarized by Blackwood, 1971, and by Kaufman and Catalano, 1979). Autopsy data were reported in 46 cases. In the autopsied cases all specific diagnoses were confirmed (26 cases); 2 of 4 cases reported as normal on biopsy were found to be normal at autopsy; in 1 case there was an active meningoencephalitis that had been missed; in the other case, cerebellar atrophy. The significant problem was the 16 cases in which biopsies were abnormal but not specific. At autopsy, 4 continued to show nonspecific findings, and there was 1 case of white matter disease (Schilder's). Tumors were present in 5 cases; all of these cases were pre-CT scan and probably would be diagnosed by imaging. But here were also 4 cases with diffuse diseases not diagnosed on biopsy, including 2 cases of lipidoses and 2 cases of Creutzfeldt-Jakob disease. Hence, in terms of specific diffuse diseases, there were no false positives but 5 of 46, or about 11 percent, false negatives and another 10 percent without specific diagnoses even at autopsy.

Directly pertinent to the question of the usefulness of cerebral biopsy in patients with dementia are the four series that concentrated upon such cases. Green et al. (1952) reported the results of biopsies of 15 patients with presenile dementias. There were 7 cases of Alzheimer's, 1 case of Pick's, and 7 cases showing nonspecific changes. In the series of 59 biopsies in patients with presenile dementia reported by Smith et al. (1966), there were 34 cases of Alzheimer's, 1 combined case of Alzheimer's and Pick's, 2 Pick's, 2 vascular, 2 chronic meningoencephalitis, and 1 Creutzfeldt-Jakob. Seventeen (29 percent) biopsy cases showed no specific changes. Bowen et al. (1982) reported 36 brain biopsy samples; Alzheimer's accounted for 23, Creutzfeldt-Jakob for 1, vascular disease for 2, leukodystrophy for 1, and microglioma for 1. Eight cases had no diagnostic changes. A 23-case series of Katzman and associates (Coblentz et al. (1973), Kaplan et al. (1985), Crystal et al. (1982), and Koto et al. (1977)) included 11 Alzheimer's, 1 Pick's, 2 microinfarcts, 1 normal pressure hydrocephalus with meningeal thickening, 2 Creutzfeldt-Jakob, 1 chronic meningitis, 1 vasculitis, and 4 nonspecific. We are aware of eight autopsies; six confirmed specific diagnoses. One of the cases that had nonspecific changes on biopsy turned out to have motor neuron disease on autopsy; the other had a lacunar state. Thus in the earlier series of Green et al. (1952) and Smith et al. (1966), 24 of 74 biopsies were nonspecific and failed to provide diagnosis. In contrast, in the series of Bowen et al. and Katzman et al. the number of nondiagnostic biopsies fell to 21 percent. This may be attributed in part to the improved diagnosis of subcortical diseases by use of modern imaging methods and in part to improved understanding of diseases that produce dementia. Specifically the changes in the brain characteristic of Creutzfeldt-Jakob disease were not yet appreciated at the time of the Green et al. and Smith et al. series, nor had the syndromes of normal pressure hydrocephalus and of multi-infarct dementia been defined at the time of the Green et al. and Smith et al. series. Overall, however, in these four series 73 percent of the biopsies gave a specific diagnosis.

b. Risks of Biopsy. Risk data are not available for the important biopsy series of Bowen et al. Data are, however, available for six series that include 437 cases. These data are heavily skewed by the Blackwood and Cumings series of 178 biopsies; these authors state: "There has been no evidence at all that the patients have suffered in any way. There was neither immediate clinical deterioration nor was there post-operative death in any case. There was no evidence of post-operative epilepsy or haemorrhage, or infection." Perhaps this salutary experience explains why biopsies are more readily carried out in

Great Britain. In the remaining 259 cases (series of Green et al.; Groves and Møller; Smith et al.; Kaufman and Catalano; and Katzman) (Table 7) there were three postoperative deaths (two associated with postoperative hemorrhage, one a cardiac arrest in a 15-month-old who also underwent ventriculography), and there were 10 instances of morbidity--none resulting in permanent neurological deficit. In the entire 437 cases the overall mortality was 0.75 percent and morbidity 2 percent. If one considers only the three dementia series included there was one death in 96 biopsies, or about a 1 percent mortality rate, and three instances of postoperative morbidity, a 3 percent rate. If in fact there has been no morbidity in the Bowen series then these percentages would be reduced by about one-third.

An additional risk not to be found in these statistics is that of spreading infection of the latent virus disorder, Creutzfeldt-Jakob disease. Instances of spread by improperly sterilized instruments which are used in subsequent brain operations has been documented (Bernoulli et al., 1977). However, the parameters for adequate chemical as well as heat sterilization have now been established and are used in most neurosurgical operating rooms (Traub et al., 1974; Gajdusek et al., 1977; ANA, 1986).

c. Role of Biopsy. Cerebral biopsy has played a critical role in advancing knowledge of dementias. The classical description of the ultrastructural changes in Alzheimer's disease in the early 1960s by Terry (1963) and by Kidd (1964) required the availability of fresh tissue obtained at cerebral autopsy. The extensive biochemical studies of Bowen and colleagues that have established the changes in the acetylcholine and other neurotransmitter systems early in the course of Alzheimer's required biopsy tissue. In the immediate future, Alzheimer biopsy material may be needed for the adequate study of the molecular biology of the disease and for determining what genes are expressed in the diseased brain, information that will be necessary for an understanding of pathogenesis and that may help in determining etiology. In addition, cerebral biopsy has led to the delineation of the pathology characteristic of several unusual but important disorders that present with dementia.

The use of cerebral biopsy for diagnosis has been more controversial. One concern is that 20 to 25 percent of the biopsies will not produce a specific diagnosis. In most instances when an autopsy has been carried out in patients with nonspecific diagnoses, unusual disorders have been found which reflect the selected nature of patients being referred for this procedure. Although the numbers are small in these series, there was no instance of a case in which the biopsy was nondiagnostic and the autopsy showed Alzheimer's. In our experience, histological changes on biopsy are often dramatic, even in early cases. Thus the procedure does have significant diagnostic usefulness. One could raise the issue of whether this would be a cost-effective approach. A second concern is the risk; this has been extraordinarily variable between series and undoubtedly increases in relationship to the degree of cognitive impairment of the patient. In our own series two of the three instances of postoperative morbidity were due to bleeding at the operative site resulting in subdural hematomas. In both instances the patients had advanced dementia and large ventricles and were being considered for ventricular shunts; as indications have changed they would no longer be considered as suitable candidates for ventricular shunting. Nor would they have been considered to be suitable candidates for diagnostic biopsy alone. The third instance of postoperative morbidity was a prolonged bout of asceptic meningitis in a patient with isolated primary cerebral vasculitis. The three deaths that were reported in the series of 437 biopsies were all from the 1960s or earlier. It seems reasonable in the absence of larger recent series to assume a mortality of about 0.5 percent. Under these circumstances it is likely that diagnostic biopsies at present will be used sparsely in the United States and reserved for cases that are difficult to diagnose. The situation will change radically if a therapy with efficacy but significant side effects were developed (an example would be a drug that had to be administered by intraventricular cannula); then the risk of biopsy would be quite reasonable. Until that occurs Biemond's criteria (1966) still hold: when the patient has a progressive disorder with dementia and "all other possible diagnostic methods have already been tried and failed to provide sufficient diagnostic certainty; the general condition of the patient permits it..." Biemond also recommended that "modern diagnostic possibilities are exploited to the fullest in the examination of the material obtained."

3. Limits of Autopsy Certainty

Alzheimer was both a psychiatrist and anatomist and his description of the case that proved to be the prototype of Alzheimer's disease included both a description of symptoms and of changes in brain tissue. A 1984 NIA conference on diagnosis of dementia emphasized that Alzheimer's is truly a clinical pathological diagnosis dependent upon the presence during life of dementia and upon the typical pathology--silver staining neurofibrillary tangles and neuritic plaques--at biopsy or autopsy (Khachaturian, 1985). In most autopsied cases the pathological changes are so evident that there would be full agreement among pathologists concerning the diagnosis. However, in a few cases pathological changes are very mild. This creates uncertainty because the brains of nondemented elderly (Tomlinson, 1977; Ulrich, 1985) may show a few neurofibrillary tangles in the hippocampus or amygdala or an occasional neuritic plaque in the cerebral cortex. The NIA conference (Khatchaturian, 1985) recommended specific autopsy criteria for the diagnosis of Alzheimer's disease. Samples for microscopy should be stained with the Bielschowsky silver technique, thioflavin S method (with ultraviolet illumination), or the Congo red technique (polarized light), as these methods are highly sensitive. To compensate for an inadequate history and to assure a separation greater than 95 percent of Alzheimer's disease from normal aging changes, the panel recommended that the diagnosis be made if the number of neuritic plaques exceed 15 per 1 mm^2 of microscopic field in patients older than 75, exceed 10 in patients between 65 and 74 years old, exceed 8 in patients between the ages of 50 and 64, and exceed 2 in patients under 50. In addition, neurofibrillary tangles anywhere in the neocortex should not be present in patients under 75. The report (p. 1103) states "In the presence of a positive clinical history of AD these criterias should be revised downwards, although to what extent remains to be determined by future research. One suggestion was that one might only need 50 percent as many lesions in neocortical samples to retain a high confidence for the histological diagnosis."

Another limitation of autopsy accuracy occurs due to a small percentage of cases--perhaps about 5 percent in the typical series--in which there is an absence of pathological change in the brains of patients known to be demented during life. Such cases are represented in 4 percent of autopsies of the Tomlinson (1977) series, 11 percent of the Sulkava et al. (1983) series, and 6 percent of the Terry et al. (R. Terry, personal communication, 1985) series. In the latter series, 6 of 101 autopsies of quite elderly (average age 85) nursing home patients belonged in this category. The traditional neuropathological studies were supplemented with quantitative counts of nerve cells remaining in cerebral cortex and with measurements of markers of the cholinergic system and the somatostatin system. All were within limits of normal relative to age-matched brains. Such cases may represent neurodegenerative disorders whose pathology cannot be demonstrated by the typical stains (which, in the case of the Terry et al. series, include H & E, silver, and thioflavin stains) or biochemical measurements. However, it is also possible that at least some of these cases represent metabolic or toxic dementias that were potentially reversible and were not diagnosed during life. Thus the existance of such cases reflects the limitations of current diagnostic accuracy.

4. New Technologies

a. MRI. Magnetic resonance imaging (MRI) was approved for reimbursement by Medicare on January 1, 1986. MRI images are spectacular in the amount of anatomic detail that can be visualized. It is possible that MRI will eventually replace CT as the primary imaging technique but there is not yet sufficient experience to warrant this change.

MRI may be especially effective in diagnosis of multi-infarct dementia, lacunar states, and Biswanger's disease, all forms of vascular dementia, because it is so sensitive to alterations in tissue structure produced by vascular lesions. In fact, the current problem is that vascular and white matter changes are seen in some asymptomatic persons and limits of normal have yet to be defined. MRI correlation with autopsy findings is needed. The vascular etiology of dementia may become an MRI diagnosis. The current cost of an MRI is about $700.

b. Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). The development of PET using a fluorine-18-labeled cogen of glucose has made it possible to examine brain metabolism in specific brain regions during life. This dramatic new technology has been used to examine Alzheimer patients at different stages of their disease. There is evidence that memory changes may precede measurable metabolic changes (Cutler et al., 1984, 1985). However, it has been found that in relatively early cases an asymmetric but bilateral reduction in metabolism in parietal cortex is present (Friedland et al., 1985a,b); later there is a dramatic reduction in metabolism throughout the cerebral hemispheres. Experience is still too limited to know how useful the biparietal pattern may be in diagnosis. The potential usefulness of PET as a clinical diagnostic tool is limited by the short half-life of positron-emitting isotopes (about 90 minutes for fluorine 18) and the need for a local cyclotron with a team of physicists and radiochemists.

SPECT, however, has been touted as a "poor man's PET." SPECT cannot be used at present for metabolic measures but it can be used to measure truly regional blood flow accurately using iodine-123-labeled compounds that are commercially available. SPECT equipment is within the range of capital expenditures that most hospitals can make; moreover, there are many nuclear medicine specialists capable of using SPECT whose skills are underutilized because CT and MRI have displaced isotope scanning in many instances (for example, the brain scan is no longer used). Hence there is great interest on the part of such specialists in this new technique. Nevertheless, there is need for great caution. The sensitivity and specificity of SPECT measurements of blood flow in the diagnosis of dementia has not been determined. This is a matter of public health interest because the total expenditure for SPECT might be very large at a time when justification of its use is in doubt.

c. Biological Markers. The identification of a specific biological marker of Alzheimer's disease that can be used clinically would be a most important advance in the diagnosis of this disorder. This area has recently attracted the attention of many sophisticated laboratories. Two major types of markers are being investigated: 1) cerebrospinal fluid changes reflecting altered brain neurotransmitters or abnormal proteins; 2) peripheral markers, reflecting changes in skin or blood cells. The first is straightforward conceptually, but so far disappointing. The second approach is based on the assumption that systemic changes occur in Alzheimer's disease, changes that have not been demonstrated pathologically or biochemically. A number of very reputable investigators have claimsdcsassesa in finding such peripheral markers, but most attempts have not yet been replicated and there is no consensus yet as to their potential usefulness as diagnostic markers. Specifically, none of the changes reported have been shown to differentiate normal patients from Alzheimer patients early in the course of the disease. Nor is it certain whether any proposed marker distinguishes Alzheimer's disease from other brain disorders.

Markers reflecting brain changes. Thal (1985) and Thienhaus et al. (1985) have recently reviewed the extensive data available on cerebrospinal fluid (CSF) changes in dementia. The enzyme acetylcholinesterase is decreased in cerebral cortex; some investigators have found it decreased in CSF, others have not. Thal suggests that the apparent decline in some studies may be a dilutional effect secondary to ventricular enlargement. But even if this is not the explanation, decreases in the dopamine metabolite HVA, which have been found to be consistent in a subgroup of patients and appear to be related to the severity of dementia, are also found in other disorders, notably Parkinson's disease. The neuropeptide somatostatin is markedly reduced in the cerebral cortex in Alzheimer's disease; in CSF it has been found to be decreased in some patients but not in others. Norepinephrine is often decreased in the brain of Alzheimer patients but is increased in the CSF (Raskind et al., 1984). At present, changes in neurotransmitters or their metabolites in the CSF do not appear to be likely diagnostic markers.

An interesting area still to be explored is whether one or more of the abnormal brain proteins associated with Alzheimer's disease can be found in CSF or serum. Proteins of interest include paired helical filament protein, amyloid protein, and Alzheimer-specific nucleus basalis antigen (Wolozin et al., 1986). At present none of the antibodies to these proteins have served to identify the minute quantities of these abnormal proteins that may escape from the brain. Nonetheless, the effort certainly seems worthwhile.

Peripheral markers. Possible changes in peripheral cholinergic markers have interested a number of investigators. There have been reports of changes in red blood cell and plasma choline and in fluxes in Alzheimer patients, but others have either not been able to confirm these changes or have found statistical changes that are not useful as diagnostic tests (Hanin et al., 1984; Greenwald et al., 1985; Blass et al., 1985). Changes in pseudocholinesterase and in red cell acetylcholinesterase that sometimes occur are not diagnostic (Smith et al., 1982; Chipperfield et al., 1981; Perry et al., 1982). One group of investigators found that sodium-lithium countertransport rates in red cells were elevated in Alzheimer's, but the number of subjects was small and this finding has not been replicated (Diamond et al., 1983). The susceptibility of persons with Down's syndrome to Alzheimer's disease has led many workers to seek evidence of abnormal chromosomes in lymphocytes from Alzheimer patients. Although several investigators have reported increased chromosomal fragmentation or aneuploidy in cultured cells, others have not been able to confirm this (Mark and Brun, 1973; Martin et al., 1981; Sulkava et al., 1979; Nordenson et al., 1980; Ward et al., 1979). Cook-Deegan and Austin (1983) found that the DNA content in noncultured lymphocytes was not altered in familial or sporadic Alzheimer's, making chromosomal aberration unlikely.

The most intriguing work at the present is represented by reports of alteration of function of cultured Alzheimer fibroblasts. Changes reported to occur include increased CO_2 production (Sims et al., 1985), increased superoxide dismutase (Thienhaus et al., 1984), altered calcium uptake (Peterson et al., 1985), altered intracellular calcium, and reduced DNA repair (Robison et al., 1985). Some of these reported changes are quite striking--for example, W. G. Bradley and coworkers (Robison et al., 1985) found no overlap between the rates of DNA repair obtained in Alzheimer as compared to control cultures; a change in DNA repair was also reported by Li and Kaminskas (1985). All of these reports are preliminary and one can point to possible methodological flaws (for example, some of the Alzheimer patients may have received neuroleptics whereas controls have not; some of the Alzheimer patients may have become cachetic and the controls not; additional control groups are needed, including cells from patients with other neurological diseases; some of the studies have used fibroblasts from the NIA repository, cells obtained from highly selected families who may be atypical). Nevertheless, the changes reported are sufficiently dramatic to warrant a high priority pursuit of these findings. If one of these changes turns out to be specific for Alzheimer patients it would not only be an important diagnostic marker but might also provide a clue as to etiology.

Another important approach is the search for genetic markers for Alzheimer's disease. Based upon studies of families in which Alzheimer's disease has appeared for several generations, it is assumed that a dominant autosomal gene predisposing to this disorder is present. Several groups are now attempting to use the sophisticated methodology currently available for locating genes (employing RFLPs, restriction fragment length polymorphisms), methodology that was so successful in locating the Huntington gene, to study Alzheimer's disease. This approach may not work if several genes produce Alzheimer's disease; moreover, it may be quite difficult because of the late age of onset of Alzheimer's, creating uncertainty as to which living members of a family are really free of disease. The use of subtraction libraries containing DNA and cDNA clones may provide alternate approaches to the molecular genetics of Alzheimer's disease.

C. Diagnostic Criteria

Specific criteria that have been developed in the past decade for the diagnosis of Alzheimer's disease and multi-infarct dementia have contributed to an improvement in diagnostic accuracy. Two widely used sets of criteria for the diagnosis of

Alzheimer's disease are compared in Table 8: the DSM-III criteria for the diagnosis of "primary degenerative dementia" (PDD) (which are similar to those suggested by Eisdorfer and Cohen, 1980), and the ADRDA-NINCDS criteria for the probable, possible, and definite diagnoses of Alzheimer's disease. The introduction of the term "primary degenerative dementia" by the DSM-III was somewhat of an anomaly since elsewhere in that manual specific and simple terms, such as "dementia," had been substituted for cumbersome phrases, such as "chronic organic brain syndrome." DSM-III states that PDD is intended to include Alzheimer's disease, Pick's disease, and dementias with nonspecific brain changes (the latter group referred to in this report as the "5 percent problem"). In fact, it has turned out that many investigators have used the DSM-III critieria to identify the typical case of Alzheimer's disease for research purposes; autopsy studies have shown that more than 90 percent of patients who meet DSM-III criteria for PDD have Alzheimer's disease. Most clinicians hope that in the next edition of its diagnostic and statistical manual, the American Psychiatric Association will drop the term "primary degenerative dementia" and use the term Alzheimer's disease. DSM-III criteria for PDD include the DSM-III criteria for dementia with "an insidious onset with uniformly progressive deterioration course...exclusion of all other specific causes of dementia by history, physical examination, and laboratory tests" (DSM-III, p. 126). The ADRDA/NINCDS criteria for probable Alzheimer's are similar to the DSM-III criteria but are more detailed; the ADRDA/NINCDS also allows for more variation in course, recognizing, for example, that the course is not always progressive and that plateaus may occur. Both sets of criteria are restrictive, however. Karasu (1986) noted: "Essentially DSM-III is a research oriented instrument, which requires that there be a minimum of false-positive diagnoses in order to obtain a homogeneous sample and to keep any distortion or dilution of statistical data at the lowest possible level." This it succeeds in doing with its criteria for PDD/Alzheimer's. Karasu continues: "In contrast, clinical practice must insist on a minimum of false-negative diagnoses."

This latter statement is appropriately applied to the DSM-III criteria for Alzheimer's disease because there are many patients with autopsy- or biopsy-proven Alzheimer's disease who do not meet the criteria. For example, some patients will present with impairment of only one area of cognition (e.g., memory, language, or right parietal lobe deficit) (Katzman, 1985; Crystal et al., 1982). Not infrequently an Alzheimer patient may have a coexistent disorder that by itself may produce dementia (e.g., hypothyroidism), but treatment is found not to slow the progression of the cognitive loss. The report of the ADRDA/NINCDS committee on the diagnosis of Alzheimer's disease recommended that patients with an atypical course, findings, or coexistent disease be diagnosed as "POSSIBLE ALZHEIMER" (McKhann et al., 1984).

Because the designation of possible Alzheimer's is so recent, there are as yet no follow-up reports on its validity. This same report reserved the designation of "DEFINITE ALZHEIMER" for cases with biopsy or autopsy confirmation. The ADRDA/NINCDS report used the term "PROBABLE ALZHEIMER" for patients who meet criteria similar to those of DSM-III.

DSM-III also included criteria for the diagnosis of multi-infarct dementia. These criteria include the presence of dementia, "a stepwise deteriorating course [i.e., not uniformly progressive] with 'patchy' distribution of deficits early in the course...focal neurological signs and symptoms...evidence...of significant cerebrovascular disease" (DSM-III, p. 128). Relatively few patients are found to meet these criteria exactly. It has been found that scoring systems, introduced by Hachinski (1978) and modified by Rosen et al. (1980), have been of much greater utility for diagnostic purposes. However, these "ischemic scores" have so far only been validated retrospectively and a prospective autopsy series needs to be carried out. A defect of these scoring systems is that patients with pure multi-infarct dementia as well as patients with combined multi-infarct dementia and Alzheimer's disease will score similarly. Also, clinicians now find that evidence of infarct or lacunes (a lacune is a small hole in the brain--less than 15 mm in diameter--resulting from destruction of a small region of brain tissue due to the occlusion of a small artery deep in the white matter or adjacent nuclei (gray matter), a region where there is inadequate collateral circulation and many small arteries are "end arteries") on CT scan is helpful in the diagnosis and MRI may provide specific laboratory confirmation of multi-infarct dementia, although not differentiating patients with multi-infarct dementia and Alzheimer's. New criteria taking into account these techniques need to be formulated. At present the accuracy of the diagnosis of multi-infarct dementia cannot be determined.

D. Diagnostic Errors: Current Status

There is every indication that the current workup combined with the use of specific diagnostic criteria has greatly improved the clinical differential diagnosis of dementing disorders in the middle or later stages of these disorders. Larson et al. (1985) reported confirmation of specific clinical diagnoses by autopsy data obtained during a retrospective study of 200 patients with suspected dementia who had been referred to a specialized geriatric outpatient evaluation clinic. Each patient underwent an intensive evaluation including the diagnostic workup described above, and a consensus diagnosis was obtained on each. There were 37 deaths and 17 autopsies. Fifteen patients diagnosed clinically as Alzheimer's had the diagnosis confirmed; 3 of the 15 patients had pathological evidence of Parkinson's disease in addition to Alzheimer's and the coexistence of Alzheimer's and Parkinson's disease had been recognized in two of these patients during life. Correct diagnoses were also made in the remaining 2 patients, 1 with changes consistent with alcoholism, the other with Parkinson's disease without Alzheimer's. These data are encouraging. Unfortunately the results cannot yet be generalized. These patients were evaluated after 3.5 years of symptoms, and they demonstrated scores on the MMSE in the moderately impaired range. Hence the data may not be applicable to the early diagnosis of mildly impaired patients. Moreover there is an evident selection bias in this sample. There was a paucity of patients with diagnoses seen in other series; specifically, only 1 percent of the cases had multi-infarct dementia, there were no cases of normal pressure hydrocephalus or brain tumor, and no indication of cases of Creutzfeldt-Jakob disease or Huntington's chorea, all of which are present in prospective series and in large autopsy series. Perhaps diagnoses of such conditions had been made by other physicians, reducing the likelihood of the families of patients with predominantly neurological conditions seeking the services of this clinic.

There are additional autopsy data in regard to the accuracy of the diagnosis of Alzheimer's disease or "primary degenerative dementia" (DSM-III equivalent of Alzheimer's) in patients who meet research diagnostic criteria. In three prospective series, such patients have been followed to autopsy; in the Berg (Berg et al., 1984) series 6 of 6 diagnoses were confirmed at autopsy, in the Raskind (personal communication) series, 13 of 14 diagnoses were confirmed, and in the Sulkava et al. (1983) series, 22 of 27 were found to have Alzheimer's. The missed diagnoses include Creutzfeldt-Jakob disease and Parkinson's disease, as well as two instances of subcortical gliosis and two without specific changes. If generally applicable, this experience would indicate that clinical diagnoses carried out under these optimal conditions approaches a 90 percent level of accuracy, a level of accuracy that probably exceeds that reached by physicians for most diseases. This 90 percent level of diagnostic accuracy is particularly striking when compared to that reported by Jellinger (1976) from the Neurological Institute of the University of Vienna. Jellinger had obtained 1009 autopsies in patients who had been found to be demented during life. Clinical diagnoses of these patients during life included presenile (163 cases) and senile (286 cases) dementia and cerebral atherosclerosis (560 cases); when compared to the pathological diagnoses, 45.3 percent of the clinical diagnoses of presenile dementia (including pathologically Alzheimer's and combined Alzheimer's and multi-infarct dementia cases) were correct, 77.6 percent of the diagnoses of senile dementia were correct and 49.9 percent of the diagnoses of cerebral atherosclerosis were correct (here accepting combined Alzheimer's and multi-infarct dementia cases as correct diagnoses) so that overall accuracy was 65.3 percent. One can speculate that the availability of specific criteria and increasing clinical awareness of the differential diagnosis of dementia has greatly improved diagnostic accuracy.

E. Summary--Differential Diagnosis

Subsequent to a diagnosis of dementia the responsibility of the physician is to identify which of the 70-plus conditions that may cause dementia is present. There is now a consensus that an adequate differential diagnosis requires a careful and thorough clinical evaluation, CT scan, and blood tests; in special circumstances a variety of other procedures, including lumbar puncture, electroencephalogram, and other tests, may be needed. On the other hand, there are other procedures which are interesting from a research perspective but whose diagnostic use has not yet been justified, procedures such as measurement of cerebral blood flow and positron emission tomography.

A major thrust of this work is to identify those conditions which may be treatable, such as normal pressure hydrocephalus, and those conditions which are potentially reversible, such as dementia secondary to drug intoxication or metabolic derangements. The clinical workup of the patient may cost close to $1000; however, the diagnostic workup is cost-effective (before consideration of the enormous impact on patient and family) if the result is identification of those cases with treatable and reversible causes.

Cerebral biopsy can provide a specific and definitive diagnosis in about three-quarters of the cases in which it is carried out. Because no specific diagnosis is reached after intensive microscopic study of the tissue in one-quarter of the cases and because a 1 percent serious postoperative complication rate has been reported, this procedure is not widely used. Nevertheless, it can be a useful test in determining the diagnosis in cases in which significant diagnostic uncertainty exists. As potent medications for treatment of Alzheimer's disease are discovered and precise diagnosis is needed, cerebral biopsy may need to be used more frequently in the future.

The most important conditions that produce dementia are Alzheimer's disease, which accounts for more than one-half of the cases, and vascular or multi-infarct dementia, which accounts for another 10 to 20 percent of the cases. Specific clinical criteria have proved to be useful in improving the diagnoses of these conditions; thus, autopsy studies have shown a 90 percent clinical diagnostic accuracy in cases in which DSM-III criteria are met. There are, however, many patients with Alzheimer's disease who do not meet these diagnostic criteria. Also, it is difficult at our present state of knowledge to correctly identify patients who have both Alzheimer's disease and another dementing condition, particularly multi-infarct dementia or Parkinson's disease. In each of these situations a peripheral marker for Alzheimer's disease would be very useful. The search for such markers should have a high priority.

III. PROGNOSIS AND PROGNOSTIC ACCURACY

That the course of dementing illnesses is progressive and malignant, leading to early death, has been recognized for more than three decades, and formed part of the argument for differentiating dementing illness from other behavioral afflictions of the elderly (Roth, 1955; Katzman, 1976; Wang, 1978).

A. Estimates of Life Expectancy and Mortality

Wang (1978) compared the duration of disease and survival reported in several pathological series in the 1960s to survival anticipated from life tables: patients with senile dementia (mean age of onset 71.3 years) survived on the average 6.0 years, half of the expected survival of 11.1 years; patients with presenile dementia (mean age of onset 53.8 years) survived 6.9 years against an expected survival (based on the life statistics of an age- and sex-matched group) of 22.3 years; and patients with vascular dementia (mean age of onset 66.8 years) survived 3.8 years with an expected survival of 13.4 years. In the most recently published series, Barclay et al. (1985a,b) reported a mean survival time in Alzheimer patients of 8.1 years and 6.7 years in patients with multi-infarct dementia. Life expectancy in males is particularly affected. Barclay et al. found that at 5 years after diagnosis of Alzheimer's disease the actual survival relative to the anticipated survival of an age- and sex-matched group is about 60 percent in females and about 25 percent in males. This low rate of survival of males with dementia may in part account for mortality differences between Alzheimer and multi-infarct patients because there is a higher proportion of males in the multi-infarct dementia group. The fact that mean survival was increased in Barclay's 1985 series as compared to Wang's 1960s series is consistent with the improved life expectancy of the elderly and better care for dementia patients, a phenomenon that Gruenberg has termed "the failures of success" (1977, 1978).

B. Predictors of Mortality

It is evident from these studies that dementia is a predictor of death and this has been confirmed in a variety of reports. Nielsen et al. (1977), who carried out a 15-year follow-up of the entire population of a Danish island, found that those with severe dementia at the beginning of the study were all dead within 5 years, and that survival was significantly shorter for both males and females with dementia. Similar results were obtained in a study of a large (500-bed) nursing home by Peck et al. (1978). In the same nursing home, Vitaliano et al. (1981), using a dichotomous (branching, two-choice) model, found that the presence of dementia, age over 80, and being male predicted mortality. In the Vitaliano study, functional status (also treated dichotomously) was not a predictor of death; T. Brown et al. (unpublished) found, on the contrary, that the Blessed et al. functional scale was the best predictor of mortality. Additional studies using sensitive functional scales are needed in this regard.

Bronchopneumonia was the major cause of death in dementia patients in the nursing home study, an observation previously noted by Kay (1962). Peck noted (Peck et al., 1978; p. 307) that "Inability to communicate one's medical and nursing needs diminishes the prospect of being treated adequately by others, professionals and nonprofessionals."

C. Functional Decline

1. Course

Alzheimer's disease is characterized by progressive cognitive and functional decline. The disease may progress from a point where there are only mild cognitive deficits in a still functioning individual to the stage where the patient becomes mute, incontinent, and must be dressed, bathed, and fed. The decline is more or less continuous although quite variable between individuals. This variability must be emphasized. An early edition of Merritt's A Textbook of Neurology (1973) describes the course of the disorder as between 1 and 20 years. We have documented individuals with autopsy-proven Alzheimer's who have gone from mild forgetfulness to inability to give their name in 1 year and individuals with autopsy-proven Alzheimer's and mild dementia who showed no change on mental status scores over a 2-year period. In most individuals cognition and function decline together, but there are again significant individual differences; for example, one occasionally finds patients whose measured cognitive impairment is so great that they cannot give their own name yet are able to care for most activities of daily living without help.

2. Stages

Despite the variability in rate of progression and in individual cognitive functional components, it is sometimes convenient to characterize "stages" of the disorder. The most commonly used classifications are the Clinical Dementia Rating (CDR) devised at Washington University (Hughes et al., 1982) and the Global Deterioration Scale (GDS) devised by Reisberg et al. (1983).

Are there predictors (other than age and sex) of the rate of functional decline and of mortality? The data available from longitudinal studies are scanty. Information from the Duke longitudinal study suggested that changes in EEG occipital domain frequency, the WAIS deterioration quotient, and neurological changes were predictive (Wang, 1978). Berg et al. (1984) did not find EEG predictive, nor were changes on the CT scan or visual evoked responses predictive; the best predictors in their study were WAIS subtest scores, especially the digit symbol subtest, and an aphasia battery. Both Chui et al. (1985) and Mayeux (Mayeux et al., 1985) found that the presence of myoclonus and extrapyramidal signs unrelated to medication indicated poor prognosis.

Reisberg et al. (1983) reported a follow-up study of 41 community-residing Alzheimer patients. Although the numbers are small, the data may be of some practical use. Six patients died and six patients were institutionalized over an average 2-year period. Patients with only subtle clinical evidence of a decrement in cognitive performance (Global Deterioration Scale

Scores of 2 and 3) could be expected to be alive and residing in the community over a 2-year period. Patients who had begun to show functional deficits in such areas as shopping and handling their own financial affairs had a "guarded" prognosis: more than one-quarter of such patients either died or required institutionalization.

Although there is a paucity of information regarding the course and prognosis of Alzheimer's disease, longitudinal data concerning other dementias are almost nonexistent. Barclay et al. (1985a,b) found that patients with Alzheimer's disease and patients with multi-infarct dementia had comparable progression of behavioral and cognitive impairment and need for home care or institutionalization. This is in accord with findings in the Bronx Aging Study and in our own experience. We reviewed the extensive literature available on the results of placement of shunts in patients with normal pressure hydrocephalus (Katzman, 1977). Approximately 55 percent of patients showed significant improvement after surgery but this was in part offset by a 40 percent complication rate. As far as we are aware, there has been no long-term follow-up of such patients. Even more striking is the lack of data concerning patients with other forms of "reversible" dementia. We have already described evidence suggesting that some of the patients diagnosed as having pseudo-dementia later presented with a frank dementia presumably of the Alzheimer type. Larson et al. (1984) diagnosed reversible dementias in 15 of 107 dementia patients. Eleven of these 15 showed initial improvement when treated. But only 3 patients with potentially reversible dementia became completely normal; their diagnoses included subdural hematoma, medication toxicity, and rheumatoid vasculitis. Particularly discouraging was the finding that 8 of the 15 patients with reversible dementia followed for more than 2 years developed progressive deterioration consistent with an Alzheimer-type dementia. The initial diagnoses of these patients included hypothyroidism (3), subdural hematoma (1), and medication toxicity (4). Thus it appears that patients with subclinical Alzheimer's may be more likely to develop excess disability with coincident metabolic or intracranial processes. However, even if improvement is short-lived, diagnosis and treatment are certainly desirable.

3. Excess Disability

Yesavage (1985) has emphasized the importance of excess disability that may occur when a patient with Alzheimer's or multi-infarct dementia has a concurrent depression, infection, or other medical condition. Larson et al. (1984) in their follow-up of 107 dementia patients noted 5 patients with the diagnosis of irreversible dementias who improved cognitively when coexistent diseases including congestive heart failure, depression, anemia, and Parkinson's disease were treated. These 5 patients remained demented but improved cognition was measurable on the Mini-Mental State examination and the dementia rating scale. Removal of excess disability is important in improving function but there is no evidence that it alters the overall course of these disorders.

D. Predictors of Institutionalization

In considering predictors of institutionalization, one must distinguish between patients who live essentially alone in society --a significant proportion of the elderly--and those who live with family, one of whom acts as caregiver. The isolated patient may quickly reach a point where he or she cannot cope with such exigencies as shopping for food and requires help either from a companion or attendant or by being placed in a nonmedical facility, such as a board and care unit. Dementia patients with caregivers often remain at home until quite late stages of the disorder. The caregiver of a dementia patient is often a husband, wife, sister, daughter, or occasionally a friend or son. The high level of devotion that characterizes home care is suggested by the title of the standard manual, aptly titled *The 36-Hour Day* (Mace and Rabins, 1981). The predictors of nursing home placement in such circumstances are not the degree of cognitive impairment but the behavioral changes that result from the impairment and, more so, the ability of the family or other caregivers to cope. Thus in a study of 14 married male patients with Alzheimer's disease, the items most closely associated with nursing home placement were incontinence of bladder and bowel, inability to speak coherently, and inability to bathe and groom oneself (Hutton et al., 1985).

IV. PUBLIC HEALTH CONSEQUENCES OF MISDIAGNOSIS

A. Misdiagnosis of Dementia Syndrome

There is little doubt that the most dramatic impact of misdiagnosis occurs when a reversible cause of dementia is ignored. Consider the following 1985 misdiagnosis (case observed by one of the authors) that occurred in a Veterans' Administration (VA) medical center that serves as a teaching hospital for a major university. A 65-year-old World War II veteran was readmitted to the alcohol unit of the VA because he could no longer be cared for at a room and care facility. The patient, a single male, had been a successful university administrator elsewhere and had served as dean for student admissions; during an administrative upheaval in 1971 he had resigned in protest anticipating that he could obtain a similar job elsewhere. When the expectation was not met he was employed in temporary capacities, became depressed and admittedly alcoholic, depending in part on help from his family. He did not, however, develop such complications of alcoholism as cirrhosis or delirium tremens. He had been admitted to the VA 6 months earlier because of increasing memory problems and some difficulty in walking; his symptoms were attributed to his alcoholism and he was placed in a board and care unit. He quit drinking at this time but symptoms progressed; when readmitted it was found he could no longer walk without assistance and was sometimes incontinent. Admission to the VA skilled nursing facility was arranged. A neurological consultant, called just before transfer to the nursing facility, noted the coincidence of gait apraxia, incontinence, and a dementia characterized primarily by partial disorientation and impairment of recent memory but intact language function. Review of the CT scan showed large ventricles which had been interpreted as indicative of atrophy. A diagnosis of normal pressure hydrocephalus was made and confirmed with isotope cisternography. Following a ventricular shunt to drain away the excess spinal fluid, gait promptly returned to normal, incontinence disappeared, and mental status examination became normal, although the patient felt that his memory was not intact. Because of the years of dependency, plans for discharge to his board and care facility have been arranged. The impact of the correct diagnosis in this case on the patient and upon the VA health system is evident. If one assumes only a 5-year period of life in the community rather than in a skilled nursing facility, more than $100,000 will have been saved. If the diagnosis had been made at the first admission, additional savings of several thousands of dollars would have been made. These dollars hardly reflect the untold hours of nursing care that an incontinent patient would have needed. Dementias as truly reversible as in this patient probably only constitute 3 percent of dementia patients but the existence of such cases fully justifies, in monetary terms alone, a full diagnostic workup of every dementia patient. However, much of the impact of misdiagnosis on the individual, family, and society occurs in less dramatic fashion. Let us consider several of the consequences of such misdiagnosis.

1. Failure to Recognize Dementia

The most significant misdiagnosis may be failure to recognize dementia on the part of physicians who are concerned about other patient complaints. An ample number of surveys indicate that cognitive impairment in the elderly often goes unrecognized. As these surveys have not followed such patients to diagnosis, the consequences of such failures have never been systematically investigated. The potential consequences which are documented only in individual anecdotes indicate that some reversible dementias may go undiagnosed. Individuals with unrecognized progressive dementias may continue to run businesses and fail to transfer responsibilites when cognitive impairment first impairs judgement. In individual instances bankruptcies and losses of millions of dollars have occurred. A question increasingly raised in legal fights over wills is whether the deceased had Alzheimer's disease and whether the person was competent when the will was written. Individuals with early dementia who have significant professional responsibilities may make errors affecting others (for example, a radiologist who misinterprets X rays). Families will be put under stress. A spouse, not recognizing the reason for a change in behavior or personality of the afflicted person, may separate or sue for divorce. Underdiagnosis of dementia is particularly important at present as automatic retirement is no longer required. Because the incidence of dementia is so strongly age-related it becomes critical to ensure the competence of those employed in responsible positions. Some industries are beginning to recognize this; for example, the identification of impaired physicians (the impetus is fear of drug dependence) has now become an obligation of medical staffs in some states. But society has not yet dealt with the need for periodic examination, the use of sensitive mental status tests, and other approaches to this problem.

2. Normal Aging and Dementia

A very different set of consequences occurs if normal aging is misinterpreted as dementia (as occurs in up to 5 percent of some referral series). A person so diagnosed may seek early retirement. Family plans may revolve around the wrongful presumption of progressive disability. The effects are particularly devastating in families with prior experience with Alzheimer's disease who fear the incident as another example of familial Alzheimer's; yet this is a situation in which a misdiagnosis is more likely to occur.

In earlier decades senile dementia was viewed not as a disease but as a concomitant of advanced age. The common stereotype of an elderly individual included reduced mental capacity, leading to reduced expectations as well as reduced demands on the aging individual. But the boundary between normal and pathological aging is being redrawn as a consequence of our recognition of dementia as a disease. We now accept older individuals in responsible roles, including that of political leadership. Mandatory retirement age even for airline pilots is disappearing. In this environment there is now a need to define more precisely the boundary between normal aging and dementia.

3. Depression and Dementia

The misdiagnosis of depression and dementia is an occurrence that has attracted particular medical attention. It is evident that if a patient with depression is inadequately treated then there will be unnecessary disability. However, there has been so much emphasis upon this possible misdiagnosis that most patients with both depressive and cognitive symptoms will at least receive a trial of antidepressant medication. Reding et al. (1985) have called attention to a small group of patients in whom Alzheimer's disease had been underdiagnosed, in whom a diagnosis of "pseudodementia" has been incorrectly given. The consequences of this misdiagnosis might be similar to that of the veteran described earlier but may not be as great as in other cases of failure to recognize dementia since a different form of behavioral impairment will have been recognized and a patient is unlikely to have been permitted to continue with significant responsibilites until a trial of therapy is concluded.

4. Delirium and Dementia

Jarvik (1980) has pointed out the importance of the diagnosis of delirium which, if the underlying disease is untreated, carries on the one hand a mortality of up to 40 percent and on the other hand can often be completely alleviated if proper diagnosis and treatment are carried out.

There is little likelihood of delirium and dementia being confused with each other in younger patients, but in the very elderly delirium may be dismissed as a chronic dementia, resulting in inappropriate treatment. There are no adequate studies of the rate of such misdiagnosis although all physicians who treat the elderly are familiar with instances in which this has occurred. Physician education would appear to be the most important mechanism available to prevent this misdiagnosis from occurring.

B. Misdiagnosis of Dementing Disorders

1. Misdiagnosis of "Reversible and Treatable Conditions": Drugs, Metabolic Disorders, Nutritional Deficiency, Normal Pressure Hydrocephalus, Subdural Hematomas, Infections

The importance of such conditions was noted by the NIA task force on reversible dementias (1980). Such conditions may account for up to 15 percent of patients with dementia. Recently two studies of the outcome of treatment of "reversible" conditions have been published (Larson et al., 1984; Freemon and Rudd, 1982) Unfortunately only a minority of such persons return to normal; in the Larson et al. (1984) study the figure was just under 3 percent of the total dementia sample. However, two-thirds of the patients with such diagnoses improved in these two series. Thus one can estimate that dementia can be completely reversed in 3 percent of patients and improved in an additional 8 percent of dementia patients.

2. Failure to Recognize Vascular Etiology

From a public health point of view, the failure to differentiate vascular dementia from Alzheimer's disease has little consequence at present because the course is approximately the same, although vascular dementia may have a marginally greater mortality if age and sex are taken into account. Nevertheless from a treatment point of view there may be important differences.

3. Misdiagnosis of "Nontreatable" Disorders: Impact of Failure to Recognize the Presence of Dementia and Impact of Failure to Diagnose Depression

Suppose a "nontreatable" dementia is present but there is misdiagnosis within this broad category. In the case of failure to diagnose Creutzfeldt-Jakob (CJ) disease there may be a minimal safety hazard for persons caring for the patient; but there are documented cases where corneal donation from undiagnosed CJ patients has led to later infection of the recipient. A similar safety hazard exists with postmortem use of CJ pituitary as a source of growth hormone. Although the course of CJ is usually much shorter (often in terms of months) than Alzheimer's disease, in instances where there have been proven misdiagnoses (for example, in one of the patients in Raskind's autopsy series of patients meeting diagnostic criteria for Alzheimer's), the course may be longer, that is, 2 or 3 years.

Both progressive supranuclear palsy (PSP) and Alzheimer's are irreversible and progressive degenerative diseases of the brain, but misdiagnosis of PSP as Alzheimer's may have several consequences for the family and patient because the presentation and prognosis of the two conditions are so different. The most significant cognitive symptoms in PSP are usually in memory and slowness of response; because of the slowness of the patient they appear to be much more impaired cognitively than they are. If the family mistakenly believes the patient has Alzheimer's, a condition in which the cognitive deficit reflects a loss of neurons involved in basic processes of understanding as well as memory, then they may not make the effort to communicate with the PSP patient who is in fact intact ih many intellectual spheres. On the other hand the PSP patient may have rapid progression of motor deficit and become wheelchair-bound at a time in the course of the illness when the Alzheimer patient is still quite mobile. Thus correct early diagnosis would help with the family's ability to plan for the future.

4. Misdiagnosis as Function of Age of Patient

As previously noted in the very elderly, Alzheimer's and vascular dementia constitute a greater percentage of the population of dementia patients and the reversible dementias occupy a smaller niche. For example, normal pressure hydrocephalus accounts for 5 percent of cases of dementia in patients under 70 and less than 1.5 percent of cases after age 70

(Jellinger, 1976). Nevertheless, that reversible normal pressure hydrocephalus occurs after age 70 is well documented. What is not known about this condition, or about the other reversible causes of dementia, is the proportion of cases in the very elderly in which proper diagnosis and treatment leads to significant clinical improvement.

5. Failure to Recognize Excess Disability

A number of gerontologists have recognized the role of intercurrent problems, physical illnesses, depression and anxiety, and environmental stresses in increasing the disability of patients with primary dementing illnesses (e.g., Brody et al., 1974; Yesavage, 1985). Larson et al. (1985) have documented cognitive improvement in patients with excess disability whose concurrent problems have been diagnosed and treated. The importance of such efforts needs further documentation and physicians need to be made aware of these findings.

C. Impact on Families

1. Limitation on Reimbursement as Function of Diagnosis

The limitation of reimbursement as a function of diagnosis has been of great concern to families and the Alzheimer's Disease and Related Disorders Association, in particular when the diagnosis of Alzheimer's has been considered to be a "psychiatric" diagnosis and therefore not entitled to the same reimbursement schedules as ordinary medical disorders. There is currently great interest on the part of lawmakers in rectifying this situation. If successful, the reverse might occur and Alzheimer's become a favored diagnosis. There is no doubt that such fiscal impact of diagnosis will influence the choice of diagnosis by the physician who feels that the first obligation is to the welfare of the patient. The extent to which current "misdiagnoses" represents such concern by physicians needs to be documented.

2. Home Health and Nursing Home Care

Home health and nursing home care are often not covered by Medicare or insurance carriers if the diagnosis of Alzheimer's is the primary one. It is easier to obtain care for one's patient if a diagnosis of congestive heart failure or urinary tract infection is made. Consequently the physician and family may seek secondary diagnoses to justify needed care. Again the system needs to be rationalized if diagnostic terms are to have meaning and reasonable statistics are to be obtained.

D. Diagnostic Accuracy and Public Health Policy

1. Costs

In an earlier section we analyzed the costs of the diagnostic workup. Is this diagnostic workup cost-effective from a purely fiscal standpoint or must justification rest on the social and individual benefits that accrue from correct diagnosis? Suppose we assume that a comprehensive single physician workup will cost $1100 for most patients and then we add another $150 to cover the costs of additional tests needed on a fraction of the patients, a total of $1250. The cost of diagnostic workup on 100 patients would be $125,000. This is the equivalent of the cost of five person-years of nursing home care in most jurisdictions. Based upon the conservative estimate that 3 of the 100 dementia patients have fully reversible dementias and an additional 8 have a treatable process that can be arrested, the cost of the workup on the 100 patients would be offset if these 11 patients saved on the average 5 1/2 months of nursing home care. Thus a complete diagnostic workup is likely to be more than cost-effective on a purely dollar basis. But studies confirming that this happens would be difficult to design and have not been carried out.

2. Legislation and Diagnostic Criteria for Alzheimer's Disease

Because of the recognition of the social importance of Alzheimer's disease and the public interest in this disorder, an interest fostered by local chapters as well as the national Alzheimer's Disease and Related Disorders Association, legislation specifically designed to benefit the Alzheimer patient and family members has been introduced in the Congress and in many state legislatures. Insofar as such legislation provides support for model clinics (such as the six California State-supported Alzheimer Disease and Diagnostic and Treatment Centers) or for specialized care facilities (for example, day care centers, respite centers, or special "restraint-free" units for agitated Alzheimer patients), the problem of diagnostic accuracy may not be of critical importance. The professional and community consensus is to serve patients with related disorders as well as those with

Alzheimer's and to base client selection on functional considerations. In part, this attitude is a consensus of the acknowledged diagnostic uncertainty that exists at present. If, however, legislation includes patient or family entitlement provisions and specifies "Alzheimer's disease" then our present diagnostic uncertainty would create significant problems, particularly in regard to patients with "possible" Alzheimer's disease and to patients with mixed Alzheimer's disease and depression, vascular dementia, or Parkinson's disease. Based upon the authors' clinical experience, about 40 percent of Alzheimer patients belong to these categories. Hence, at our current state of clinical knowledge it would be counterproductive to establish specific diagnostic criteria for Alzheimer's or other specific dementing disorders. It would be appropriate, however, to establish guidelines based on DSM-III for the clinical syndrome of "dementia." It would also be appropriate on the basis of our current knowledge to require a comprehensive differential diagnostic workup to ensure that resources for patients with progressive irreversible dementia are not spent on individuals with a treatable or reversible cause of dementia.

3. Workup at Nursing Home Centers

Nursing home costs account for the greater portion of the public expenditures for demented individuals. In our own studies, two-thirds of individuals in a large urban nursing home were demented and 55 percent of all the autopsies showed Alzheimer's disease. But among the demented patients in nursing homes are some with undiagnosed treatable or reversible disorders: normal pressure hydrocephalus, brain tumors, drug toxicity, or metabolic disorders. If one accepts as a reasonable goal for every patient with dementia a thorough diagnostic workup at least once in the course of his or her disease, then one must acknowledge that this goal has not been met for the majority of patients admitted to nursing homes in the past. Although this situation is constantly improving with the growing interest in dementia, it is also evident that this progress has occurred unevenly, particularly in the "old-old" patient. This situation would be significantly helped if--by legislation or regulation--a thorough diagnostic workup were required for every nursing home patient with dementia, either before admission or during the first month after admission.

4. DRGs for Physican Care of Dementia

Medicare may move to an overall physician DRG reimbursement scheme. If this does occur, a dementia DRG that allows for a full diagnostic workup, patient care, and family counseling should be considered. Under present DRG categories for inpatients, dementia patients are admitted under the category of "neurological disorder, other"--a category that would prevent the needed diagnostic workup of the dementia patients, a workup which is more costly than that for patients with certain other neurological disorders.

V. SUMMARY OF RECOMMENDATIONS

A. Physician Education Regarding Accepted Guidelines

--Use of mental status test in general medical patients.

--Workup of patients with dementia.

--Diagnostic criteria.

B. Medicare Guidelines

--Explicit statement requiring adequate workup as a protection of patient rights.

C. Diagnostic Accuracy

--Monitoring of trends in accuracy of diagnoses.

D. Development of Specific Diagnostic Tests

--Support of research seeking to identify a biological marker for Alzheimer's disease that can serve as a specific diagnostic test.

E. Research Regarding Areas of Diagnostic Uncertainty

--Research into the consequences of failure to recognize dementia (such as occurs in general medical settings).

--Longitudinal studies of outcome and prognosis of dementia patients with diagnoses other than Alzheimer's or vascular dementia.

--Clinical pathological verification of usefulness of MRI in diagnosing vascular dementias.

--Research into differential diagnosis of multi-infarct dementia from mixed multi-infarct dementia and Alzheimer's.

References

American Neurological Association, Committee on Health Care Issues (ANA), "Precautions in Handling Tissues, Fluids, and Other Contaminated Materials from Patients with Documented or Suspected Creutzfeldt-Jakob Disease," Ann. Neurol. 19:75-77, 1986.

American Psychiatric Association Task Force on Nomenclature and Statistics, Diagnostic and Statistical Manual of Mental Disorders (DSM-I), 1st ed. (Washington, D.C.: American Psychiatric Association, 1952).

American Psychiatric Association Task Force on Nomenclature and Statistics, Diagnostic and Statistical Manual of Mental Disorders (DSM-III), 3rd ed. (Washington, D.C.: American Psychiatric Association, 1980), pp. 124-126.

Antunes, L., "Nossa Experientia Actual da Biopsia do Cortex no Diagnostico Neuropsiquiatrico," Gaz. Med. Port. 16:474-476, 1963.

Balldin, J., Gottfries, C.-G., Karlsson, I., et al., "Dexamethasone Suppression Test and Serum Prolactin in Dementia Disorders," Br. J. Psychiatry 143:277-281, 1983.

Barclay, L.L., Zemcov, A., Blass, J.P., et al., "Factors Associated with Duration of Survival in Alzheimer's Disease," Biol. Psychiatry 20:86-93, 1985a.

Barclay, L.L., Zemcov, A., Blass, J.P., et al., "Survival in Alzheimer's Disease and Vascular Dementias," Neurology 35: 834-840, 1985b.

Becker, P.M., Freussner, J.R., Mulrow, C.D., et al., "The Role of Lumbar Puncture in the Evaluation of Dementia," J. Am. Geriatr. Soc. 33:392-396, 1985.

Berg, L., Danziger, W.L., Storandt, M., et al., "Predictive Features in Mild Senile Dementia of the Alzheimer Type," Neurology 34:563-569, 1984.

Bernoulli, C., Siegfried, J., Baumgartner, G., et al., "Danger of Accidental Person-to-Person Transmission of Creutzfeldt-Jakob Disease by Surgery," Lancet 1:478-479, Feb. 26, 1977.

Biemond, A., "Indications, Legal and Moral Aspects of Cerebral Biopsies," in Proc. 5th Internatl. Congr. Neuropathol., Zurich (1965) (Amsterdam: Excerpta Medica, 1966), pp. 372-375.

Blackwood, W., and Cumings, J.N., "The Combined Histological and Chemical Aspects of Cerebral Biopsies," in Proc. 5th Internatl. Congr. Neuropathol., Zurich (1965) (Amsterdam: Excerpta Medica, 1966), pp. 364-371.

Blackwood, W., "Cerebral Biopsy," in Handbook of Neurology, Vol. 19 (New York: Raven Press, 1971), pp. 680-687.

Blass, J.P., Hanin, I., Barclay, L., et al., "Red Blood Cell Abnormalities in Alzheimer Disease," J. Am. Geriatr. Soc. 33:401-405, 1985.

Blessed, G., Tomlinson, B.E., and Roth, M., "The Association Between Quantitative Measures of Dementia and of Senile Change in the Cerebral Gray Matter of Elderly Subjects," Br. J. Psychiatry 114:797-811, 1968.

Bowen, D.M., Sims, N.R., Benton, S., et al., "Biochemical Changes in Cortical Brain Biopsies from Demented Patients in Relation to Morphological Findings and Pathogenesis," in Alzheimer's Disease: A Report of Progress (Aging, Vol. 9), S. Corkin, K.L. Davis, J.H. Growdon, et al., eds. (New York: Raven Press, 1982).

Brody, E.M., Kleban, M.H., Lawton, M.L., et al., "A Longitudinal Look at Excess Disabilities in the Mentally Impaired Aged," J. Gerontol. 29:79-84, 1974.

Carnes, M., Smith, J.C., Kalin, N.H., et al., "Effects of Chronic Medical Illness and Dementia on the Dexamethasone Suppression Test," J. Am. Geriatr. Soc. 31:269-271, 1983.

Chipperfield, B., Newman, P.M., Moyes, I.C.A., "Decreased Erythrocyte Cholinesterase Activity in Dementia," Lancet 2:199, 1981.

Chui, H.C., Teng, E.L., Henderson, V.W., et al., "Clinical Subtypes of Dementia of the Alzheimer Type," Neurology 35: 1544-1550, 1985.

Coblentz, J.M., Mattis, S., Zingesser, L.H., et al., "Presenile Dementia. Clinical Aspects and Evaluation of Cerebral Spinal Fluid Dynamics," Arch. Neurol. 29:299-308, 1973.

Cook-Deegan, R.M., and Austin, J.H., "Implications of Normal Lymphocyte DNA Content in Familial Alzheimer Disease," Am. J. Med. Genet. 15:511, 1983.

Crystal, H.A., Horoupian, D.S., Katzman, R., et al., "Biopsy Proven Alzheimer's Disease Presenting as a Right Parietal Lobe Syndrome," Ann. Neurol. 12:186-188, 1982.

Cummings, J.L., and Benson, D.F., "Subcortical Dementia. Review of an Emerging Concept," Arch. Neurol. 41:874-879, 1984.

Cutler, N.R., Duara, R., Creasey, H., et al., "Brain Imaging: Aging and Dementia," Ann. Intern. Med. 101:355-369, 1984.

Cutler, N.R., Haxby, J.V., Duara, R., et al., "Brain Metabolism as Measured with Positron Emission Tomography: Serial Assessment in a Patient with Familial Alzheimer's Disease," Neurology 35:1556-1561, 1985.

Delaney, P., "Dementia: The Search for Treatable Causes," South. Med. J. 75:707-709, 1982.

DePaulo, J.R., Jr., and Folstein, M.F., "Psychiatric Disturbances in Neurological Patients: Detection, Recognition, and Hospital Course," Ann. Neurol. 4:225-228, 1978.

Devanand, D.P., and Nelson, J.C., "Concurrent Depression and Dementia: Implications for Diagnosis and Treatment," J. Clin. Psychiatry 46: 389-392, 1985.

Diamond, J.M., Matsuyama, S.S., Meier, K., et al., "Elevation of Erythrocyte Countertransport Rates in Alzheimer's Dementia," N. Engl. J. Med. 309:1061-1062, 1983.

Eadie, M., "Experience with Cortical Biopsy," Proc. Aust. Assoc. Neurol. 2:59, 1964.

Eisdorfer, C., and Cohen, D., "Diagnostic Criteria for Primary Neuronal Degeneration of the Alzheimer's Type," J. Fam. Pract. 11:553-557, 1980.

Folstein, M., Anthony, J.C., Parhad, I., et al., "The Meaning of Cognitive Impairment in the Elderly," J. Am. Geriatr. Soc. 33:228-235, 1985.

Folstein, M.F., Folstein, S.E., and McHugh, P.R., "Mini-Mental State. A Practical Method for Grading the Cognitive State of Patients for the Clinician," J. Psychiatr. Res. 12:189-198, 1975.

Folstein, M.F., and McHugh, P.R., "Dementia Syndrome of Depression," in Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7), R. Katzman, R.D. Terry, and K.L. Bick, eds. (New York: Raven Press, 1978), pp. 87-93.

Freemon, F.R., and Rudd, S.M., "Clinical Features that Predict Potentially Reversible Progressive Intellectual Deterioration," J. Am. Geriatr. Soc. 33:449-451, 1982.

Friedland, R.P., Brun, A., and Budinger, T.F., "Pathological and Positron Emission Tomographic Correlations in Alzheimer's Disease," Lancet 1:228, 1985a.

Friedland, R.P., Budunger, T.F., Koss, E., et al., "Alzheimer's Disease: Anterior-Posterior and Lateral Hemispheric Alterations in Cortical Glucose Utilization," Neurosci. Lett. 53:235-240, 1985b.

Gado, M., Hughes, C.P., Danziger, W., et al., "Volumetric Measurements of the Cerebrospinal Fluid Spaces in Demented Subjects and Controls," Radiology 144:535-538, 1982.

Gajdusek, D.C., Gibbs, C.J., Asher, D.M., Jr., et al., "Precautions in Medical Care of, and in Handling Materials from Patients with Transmissible Virus Dementia (Creutzfeldt-Jakob Disease)," N. Engl. J. Med. 297:1253-1258, 1977.

Garcia, C.A., Reding, M.J., and Blass, J.P., "Overdiagnosis of Dementia," J. Am. Geriatr. Soc. 29:407-410, 1981.

Garcia, C.A., Tweedy, J.R., and Blass, J.P., "Underdiagnosis of Cognitive Impairment in a Rehabilitation Setting," J. Am. Geriatr. Soc. 32:339-342, 1984.

Green, M.A., Stevenson, L.D., Fonseca, J.E., et al., "Cerebral Biopsy in Patients with Presenile Dementia," Dis. Nerv. Syst. 13:303, 1952.

Greenwald, B.S., Edasery, J., Mohs, R.C., et al., "Red Blood Cell Choline. I: Choline in Alzheimer's Disease," Biol. Psychiatry 20:367-374, 1985.

Groves, R., and Møller, J., "The Value of the Cerebral Cortical Biopsy," Acta Neurol. Scand. 42:477-482, 1966.

Gruenberg, E.M., "The Failures of Success," Milband Mem. Fund. Quart. 55:3-24, 1977.

Gruenberg, E.M., "Epidemiology of Senile Dementia," in Neurological Epidemiology: Principles and Clinical Application, B.S. Schoenberg, ed. (New York: Raven Press, 1978).

Hachinski, V., "Cerebral Blood Flow Differentiation of Alzheimer's Disease from Multi-Infarct Dementia," in Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7), R. Katzman, R.D. Terry, and K.L. Bick, eds. (New York: Raven Press, 1978).

Hanin, I., Reynolds, C.F., Kupfer, D.J., et al., "Elevated Red Blood Cell/Plasma Choline Ratio in Dementia of the Alzheimer Type: Clinical and Polysomnographic Correlates," Psychiatry Res. 13:167, 1984.

Hasse, G.R., "Diseases Presenting as Dementia," in Dementia, 2nd ed., C.E. Wells, ed. (Philadelphia: F.A. Davis, 1977).

Hoffman, R.S., "Diagnostic Errors in the Evaluation of Behavioral Disorders," JAMA 248(8):964-967, 1982.

Hughes, C.P., Berg, L., Danziger, W., et al., "A New Clinical Scale for the Staging of Dementia," Br. J. Psychiatry 140: 566-572, 1982.

Hutton, J.T., Dippel, R.L., Loewenson, R.B., et al., "Predictors of Nursing Home Placement of Patients with Alzheimer's Disease," Tex. Med. 81:40-43, 1985.

Jarvik, L.F., "Diagnosis of Dementia in the Elderly: A 1980 Perspective," in Annual Review of Gerontology and Geriatrics, Vol. 1, C. Eisdorfer, ed. (New York: Springer, 1980).

Jellinger, K., "Neuropathological Aspects of Dementias Resulting from Abnormal Blood and Cerebrospinal Fluid Dynamics," Acta Neurol. Belg. 76:83-102, 1976.

Jorm, A.F., and Henderson, A.S., "Possible Improvement to the Diagnostic Criteria for Dementia in DSM-III," Br. J. Psychiatry 147:394-399, 1985.

Kahn, R.L., Goldfarb, A.I., Pollack, M., et al., "Brief Objective Measures for the Determination of Mental Status in the Aged," Am. J. Psychiatry 117:326, 1960.

Kaplan, J.G., Katzman, R., Horoupian, D.S., et al., "Progressive Dementia, Visual Deficits, Amyotrophy and Micro Infarcts," Neurology 35:788-798, 1985.

Karasu, T.B., "Economic Realities Force Psychiatrists to Reevaluate All Kinds of Psychotherapies," Clin. Psychiatry News 14(2):1, 27, 1986.

Katona, C.L.E., and Aldridge, C.R., "The Dexamethasone Suppression Test and Depressive Signs in Dementia," J. Affect. Disord. 8:83-89, 1985.

Katzman, R., "The Prevalence and Malignancy of Alzheimer Disease; A Major Killer," Arch. Neurol. 33:217-218, 1976.

Katzman, R., "Normal Pressure Hydrocephalus," in Dementia, 2nd ed., C.E. Wells, ed. (Philadelphia: F.A. Davis, 1977).

Katzman, R., "Vascular Disease and Dementia," in H. Houston Merrit Memorial Volume, M.D. Yahr, ed. (New York: Raven Press, 1983).

Katzman, R., "Dementia," in Current Neurology, Vol. 5, S.H. Appel, ed. (New York: John Wiley & Sons, 1984).

Katzman, R., "Clinical Presentation of the Course of Alzheimer's Disease: The Atypical Patient," Interdiscipl. Topics Gerontol. 20:12-18, 1985.

Katzman, R., "Dementia," in Diseases of the Nervous System, A.K. Asbury, G.M. McKhann, and W.I. McDonald, eds. (London: William Heinemann/Philadelphia: Ardmore Medical), 1986, pp. 890-896.

Katzman, R., Brown, T., Fuld, P., et al., "Validation of a Short Orientation-Memory-Concentration Test of Cognitive Impairment," Am. J. Psychiatry 140:734-739, 1983.

Katzman, R., and Terry, R.D., Neurology of Aging (Philadelphia: F.A. Davis, 1983), pp. 15-50.

Kaufman, H., and Catalano, L.W., Jr., "Diagnostic Brain Biopsy: A Series of 50 Cases and a Review," Neurosurgery 4:129-136, 1979.

Kay, D., "Outcome and Cause of Death in Mental Disorders in Old Age," Acta Psychiatr. Scand. 38:249, 1962.

Kendall, R.E., "The Stability of Psychiatric Diagnoses," Brit. J. Psychiatry 124:352-356, 1974.

Khachaturian, Z.S., "Diagnosis of Alzheimer's Disease," Arch. Neurol. 42:1097-1105, 1985.

Kidd, M., "Alzheimer's Disease, an Electron Microscopic Study," Brain 87:303-320, 1964.

Kiloh, L.G., "Pseudodementia," Acta Psychiatr. Scand. 37:336-351, 1961.

Knights, E.G., and Folstein, M.F., "Unsuspected Emotional and Cognitive Disturbances in Medical Patients," Ann. Intern. Med. 87:723, 1977.

Koto, A., Rosenberg, G., Zingesser, L.H., et al., "Syndrome of Normal Pressure Hydrocephalus: Possible Relationship to Hypertensive and Arteriosclerotic Vasculopathy," J. Neurol. Neurosurg. Psychiatry 40:73-79, 1977.

Kral, V.A., "The Relationship Between Senile Dementia (Alzheimer Type) and Depression," Can. J. Psychiatry 28:304-306, 1983.

Kral, V.A., "Benign Senescent Forgetfulness," in Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7),R.Katzman, R.D. Terry, and K.L. Bick, eds. (New York: Raven Press, 1978).

Kral, V.A., and Muller, H., "Memory Dysfunction: A Prognostic Indicator in Geriatric Patients," Can. Psychiatr. Assoc. 11:343-349, 1966.

Kurtzke, J.F., Epidemiology of Cerebrovascular Disease (Berlin: Springer-Verlag, 1969).

Larson, E.B., Burton, M.P.H., Reifler, V., et al., "Dementia a in Elderly Outpatients: A Prospective Study," Ann. Intern. Med. 100:417-423, 1984.

Larson, E.B., Reifler, B.V., Sumi, S.M., et al., "Diagnostic Evaluation of 200 Elderly Outpatients with Suspected Dementia," J. Gerontol. 5:536-543, 1985.

Li, J.C., and Kaminskas, E., "Deficient Repair of DNA Lesions in Alzheimer's Disease Fibroblasts," Biochem. Biophys. Res. Commun. 129:733-738, 1985.

Lijtmaer, H., Fuld, P.A., and Katzman, R., "Prevalence and Malignancy of Alzheimer's Disease," Arch. Neurol. 33:304, 1976.

Mace, N.L., and Rabins, P.V., The 36-Hour Day (Baltimore: Johns Hopkins Press, 1981).

Mahendra, B., "'Pseudodementia': An Illogical and Misleading Concept," Br. J. Pyschiatry 143:202, 1983.

Mahendra, B., "Depression and Dementia: The Multi-faceted Relationship," Psychol. Med. 15:227-236, 1985.

Mark, J., and Brun, A., "Chromosomal Deviations in Alzheimer's Disease Compared to Those in Senescence and Dementia," Gerontol. Clin. 15:253, 1973.

Marsden, C., and Harrison, M., "Outcome of Investigation of Patients with Presenile Dementia," Brit. Med. J. 2:249, 1972.

Martin, J.M., Kellet, J.M., and Kahn, J., "Aneuploidy in Cultured Human Lymphocytes. II. A Comparison Between Senescence and Dementia," Age Ageing 10:24, 1981.

Mayer-Gross, W., "Some Symptoms of Organic Brain Disease," Arch. Psychiatr. Nervenkr. 92:433-618, 1931.

Mayer-Gross, W., and Guttmann, E., "Schema for the Examination of Organic Cases," J. Ment. Sci. 83:440-448, 1937.

Mayeux, R., Stern, Y., and Spanton, S., "Heterogeneity in Dementia of the Alzheimer Type: Evidence of Subgroups," Neurology 35:453-461, 1985.

McCallister, T.W., and Price, T.R.P., "Severe Depressive Pseudodementia With and Without Dementia," Am. J. Psychiatry 139:5, 1982.

McCartney, J.R., and Palmateer, L.M., "Assessment of Cognitive Deficit in Geriatric Patients: A Study of Physcian Behavior," J. Am. Geriatr. Soc. 33:467-471, 1985.

McKeith, I.G., "Clinical Use of the DST in a Psychogeriatric Population," Brit. J. Psychiatry 145:389-393, 1984.

McKhann, G., Drachman, D., Folstein, M., et al., "Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Groups Under the Auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," Neurology 34:939-944, 1984.

Merrit, H.H., A Textbook of Neurology, 5th ed. (Philadelphia: Lea & Febiger, 1973).

Mesulam, M-M., "Slowly Progressive Aphasia Without Generalized Dementia," Ann. Neurol. 11:592-598, 1982.

National Institute on Aging Task Force (NIA), "Senility Reconsidered. Treatment Possibilities for Mental Impairment in the Elderly," JAMA 244:259-263, 1980.

Nielsen, J., Homma, A., and Biorn-Henricksen, T., "Follow-up 15 Years After a Geronto-Psychiatric Prevalence Study--Conditions Concerning Death, Cause of Death, and Life Expectancy in Relation to Psychiatric Diagnosis," _J. Gerontol._ 32:554-561, 1977.

Nordenson, I., Adolfsson, R., Beckman, G., et al., "Chromosomal Abnormality in Dementia of Alzheimer Type," _Lancet_ 1:481, 1980.

Peck, A., Wolloch, L., and Rodstein, M., "Mortality of the Aged with Chronic Brain Syndrome II," in _Alzheimer's Disease: Senile Dementia and Related Disorders_ (_Aging_, Vol. 7), R. Katzman, R.D. Terry, and K.L. Bick, eds. (New York: Raven Press, 1978), pp. 299-308.

Perry, R.H., Wilson, I.D., Bober, M.J., et al., "Plasma and Erythrocyte Acetylcholinesterase in Senile Dementia of Alzheimer Type," _Lancet_ 1:174-175, 1982.

Peterson, C., Gibson, G.E., and Blass, J.P., "Altered Calcium Uptake in Cultured Skin Fibroblasts from Patients with Alzheimer's Disease," _N. Engl. J. Med._ 312:1063-1065, 1985.

Pogacar, S., and Williams, R.S., "Alzheimer's Disease Presenting as Slowly Progressing Aphasia," Rhode Island Med.J. 67:181-185, 1984.

Postiglione, A., Grossi, D., Faccenda, F., et al., "Non Invasive Study of Carotid Arteries by Echo-Doppler and Metabolic Abnormalities in Patients with Dementia," Angiology 36:160-164, 1985.

Rabins, P.V., "The Prevalence of Reversible Dementia in a Psychiatric Hospital," Hosp. Commun. Psychiatry 32:490-492, 1981.

Rabins, P.V., Merchant, A., and Nestadt, G., "Criteria for Diagnosing Reversible Dementia Caused by Depression: Validation by 2-Year Follow-up," Br. J. Psychiatry 144:488-492, 1984.

Raskind, M.A., Peskind, E.R., Halter, J.B., et al., "Norepinephrine and MHPG Levels in CSF and Plasma in Alzheimer's Disease," Arch. Gen. Psychiatry 41:343-346, 1984.

Reding, M., Haycox, J., and Blass, J., "Depression in Patients Referred to a Dementia Clinic: A Three-Year Prospective Study," Arch. Neurol. 42:894-896, 1985.

Reding, M., Haycox, J., Wigforss, K., et al., "Follow-Up of Patients Referred to a Dementia Service," J. Am. Geriatr. Soc. 32:265-268, 1984.

Reifler, B.V., "Arguments for Abandoning the Term Pseudodementia," J. Am. Geriatr. Soc. 30:665-668, 1982.

Reisberg, B., Shulman, E., Ferris, S.H., et al., "Clinical Assessment of Age-Associated Cognitive Decline and Primary Degenerative Dementia: Prognostic Concomitants," Psychopharmacol. Bull. 19:734-739, 1983.

Robison, S.H., Munzer, J.S., Tanden, R., et al., "Repair of Alkylated DNA Is Impaired in Alzheimer's Disease Cells," Neurology 35(Suppl. 1):217-218, 1985.

Ron, M.A., Toone, B.K., Garralda, M.E., et al., "Diagnostic Accuracy in Presenile Dementia," Br. J. Psychiatry 134:161-168, 1979.

Rosen, W.G., Terry, R.D., Fuld, P.A., et al., "Pathological Verification of Ischemic Score in Differentiation of Dementias," Ann. Neurol. 7:486-488, 1980.

Rosenberg, G.A., Kornfeld, M., Stouring, J., et al., "Subacute Arteriosclerotic Encephalopathy (Binswanger): Computerized Tomography," Neurology 29:1102-1106, 1979.

Roth, M., "The Natural History of Mental Disorder in Old Age," Br. J. Psychiatry 101:281-301, 1955.

Shapiro, M.B., Post, F., Lofbing, B., et al., "'Memory Function' in Psychiatric Patients over 60; Some Methodological and Diagnostic Implications," J. Mental Sci. 102:233-246, 1956.

Sims, N.R., Finegan, J.M., and Blass, J.P., "Altered Glucose Metabolism in Fibroblasts from Patients with Alzheimer's Disease," N. Engl. J. Med. 313(10):638-639, 1985.

Smith, R.C., Ho, B.T., Hsu, L., et al., "Cholinesterase Enzymes in the Blood of Patients with Alzheimer's Disease," Life Sci. 30:543-546, 1982.

Smith, J.S., and Kiloh, L.G., "The Investigation of Dementia: Results in 200 Consecutive Admissions," Lancet 1:824-827, 1981.

Smith, T., Turner, E., and Sim, M., "Cerebral Biopsy in the Investigation of Presenile Dementia. II. Pathologic Aspects," Br. J. Psychiatry 112:127-133, 1966.

Sulkava, R., Haltia, M., Paetau, A., et al., "Accuracy of Clinical Diagnosis in Primary Degenerative Dementia: Correlation With Neuropathological Findings," J. Neurol. Neurosurg. Psychiatry 46:9-13, 1983.

Sulkava, R., Rossi, L., and Knuutia, S., "No Elevated Sister Chromatid Exchange in Alzheimer's Disease," Acta Neurol. Scand. 59:156, 1979.

Terry, R.D., "Neurofibrillary Tangles in Alzheimer's Disease," J. Neuropathol. Exp. Neurol. 22:629-642, 1963.

Terry, R.D., Gonatas, N.K., and Weiss, M., "Ultrastructural Studies in Alzheimer's Presenile Dementia," Am. J. Pathol. 44:269, 1964.

Thal, L.J., "Changes in Cerebrospinal Fluid Associated with Dementia," in Memory Dysfunction, D. Olton, S. Corkin, E. Gamzu et al., eds. (New York: N. Y. Acad. of Sciences, 1985), pp. 235-241.

Thienhaus, O.J., Hartford, J.T., Skelly, M.F., et al., "Biological Markers in Alzheimer's Disease," J. Am. Geriatr. Soc. 33:715-726, 1985.

Thienhaus, O.J., Price, C.A., and Bosmann, H.B., "Superoxide Dismutase (SOD) in Alzheimer Fibroblasts," Pharmacol. 26:219, 1984.

Tomlinson, B.E., "Morphological Changes and Dementia in Old Age," in Aging and Dementia, W.L. Smith and M. Kinsbourne, eds. (New York: Spectrum Publications, 1977).

Traub, R.D., Gajdusek, D.C., and Gibbs, C.J., Jr., "Precautions in Conducting Biopsies and Autopsies on Patients With Presenile Dementia," J. Neurosurg. 41:394-395, 1974.

Ulrich, J., "Alzheimer Changes in Nondemented Patients Younger than Sixty-Five: Possible Early Stages of Alzheimer's Disease and Senile Dementia of Alzheimer Type," Ann. Neurol. 17:273-277, 1985.

Vitaliano, P.P., Peck, A., Johnson, D.A., et al., "Dementia and Other Competing Risks for Mortality in the Institutionalized Aged," J. Am. Geriatr. Soc. 29:513-519, 1981.

Wang, H.S., "Prognosis in Dementia and Related Disorders in the Aged," in Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7), R. Katzman, R.D. Terry, and K.L. Bick, eds. (New York, Raven press, 1978), pp. 309-313.

Ward, B., Cook, R.H., Robinson, A., et al., "Increased Aneuploidy in Alzheimer Disease," Am. J. Med. Genet. 3:137, 1979.

Wolozin, B.L., Pruchnicki, A., and Dickson, D.W., et al., "A Neuronal Antigen in the Brains of Alzheimer Patients," Science, 232:648-650, 1986.

Yesavage, J.A., Testimony at Alzheimer's Disease Task Force, State of California, UCLA, 1985.

Table 1.--Disorders Presenting as Dementia

ALZHEIMER'S DISEASE

- With or without vascular disease
- With or without Parkinson's disease
- With or without other dementing diseases

OTHER IRREVERSIBLE DEMENTIAS

Degenerative Diseases

- Pick's disease
- Huntington's disease
- Progressive supranuclear palsy
- Parkinson's disease
- Cerebellar degenerations
- Amyotrophic lateral sclerosis (ALS)
- Parkinson-ALS-dementia complex of Guam and New Guinea
- Rare genetic and metabolic diseases (Hallervorden-Spatz, Kuf's, Wilson's, late-onset metachromatic leukodystrophy, adrenoleukodystrophy)

Vascular Dementias

- Multi-infarct dementia
- Cortical microinfarcts
- Lacunar dementia
- Binswanger disease
- Cerebral embolism by fat or air

Anoxic Dementia

- Cardiac arrest
- Cardiac failure (severe)
- Carbon monoxide

Traumatic

- Dementia pugilistica (boxer's dementia)
- Head injuries (open or closed)

Infections

- Aquired Immune Deficiency Syndrome (AIDS)
  - AIDS dementia
  - Opportunistic infections
- Creutzfeldt-Jakob disease (subacute spongiform encephalopathy)
- AIDS (primary or opportunistic infections)
- Progressive multifocal leukoencephalopathy
- Post-encephalitic dementia
- Behcet's syndrome

(Tab continued)

(Table 1--Continued)

TREATABLE DEMENTIAS

Infections
- Herpes encephalitis
- Fungal meningitis or encephalitis
- Bacterial meningitis or encephalitis
- Parasitic encephalitis
- Brain abscess
- Neurosyphilis (general paresis)

Normal Pressure Hydrocephalus (communicating hydrocephalus of adults)

Space-Occupying Lesions
- Chronic or acute subdural hematoma
- Primary brain tumor
- Metastatic tumors (carcinoma, leukemia, lymphoma, sarcoma)

Multiple Sclerosis (some cases)

Auto-immune Disorders
- Disseminated lupus erythematosus
- Vasculitis

Toxic Dementia
- Alcoholic dementia
- Metallic poisons (e.g., lead, mercury, arsenic, manganese)
- Organic poisons (e.g., solvents, some insecticides)

Other Disorders
- Epilepsy
- Concentration camp syndrome
- Whipple disease
- Heat stroke

Note: Many of these disorders produce dementia in a small percentage of patients (e.g., epilepsy, tumors).

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, LA Jolla
CA 92093

Table 2.--Reversible Causes of Dementia

Psychiatric Disorders
- Depression
- Sensory deprivation
- Other psychoses

Drugs
- Sedatives
- Hypnotics
- Anti-anxiety agents
- Anti-depressants
- Anti-arrhythmics
- Anti-hypertensives
- Anti-convulsants
- Digitalis and derivatives
- Drugs with anti-cholinergic side effects
- Others (mechanism unknown)

Nutritional Disorders
- Pellagra (B-6 deficiency)
- Thiamine deficiency (Wernicke syndrome, acute phase treatable)
- Cobalamin deficiency (B-12) or pernicious anemia
- Folate deficiency
- Marchiafava-Bignami disease

Metabolic Disorders
- Hyper- and hypo-thyroidism (thyroid hormones)
- Hypercalcemia (calcium)
- Hyper- and hypo-natremia (sodium)
- Hypoglycemia (glucose)
- Hyperlipidemia (lipids)
- Hypercapnia (carbon dioxide)
- Kidney failure
- Liver failure
- Cushing syndrome
- Addison's disease
- Hypopituitarism
- Remote effect of carcinoma

Note: Most of these disorders produce dementia in only a small percentage of cases.

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, LA Jolla
CA 92093

Table 3.--Comparison of Diagnostic Criteria* for Dementia

Criteria	DSM-III	ADRDA/ NINCDS	NIA/ AMA	Jorm & Henderson
Loss of intellectual abilities...............	R	R	R	R
--Confirmed on mental status tests............		R		R
Impaired social or occupational function...	R			R
Memory impairment.........	R	R	R	R
Impairment of additional area of cognition (e.g., language, construction, praxis or personality change).................	R	+	R	+
State of consciousness not clouded--alert, awake...................	R	R	R	R
Evidence of organic factor or absence of conditions other than organic mental syndrome.........	R			R

Note: R = required, + = desirable/not required.
*SOURCES: Amer. Psych. Assoc. Task Force (1980), McKhann et al. (1984), NIA (1980), and Jorm and Henderson (1985).

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, La Jolla
CA 92093

Table 4.--Diagnosis of Dementia Syndrome: Misclassification Based on Follow-up Studies*

	Total	Orig Diag		Outcome Diag		Misclassific	
	N	Dem	Nondem	Dem	Nondem	N	%
Kendell, 1974	98	98	0	75	23	16	23
Ron et al., 1979	51	51	0	35	16	16	31
Smith & Kiloh, 1981	200	200	0	164	36	36	18
Rabins, 1981	41	41	0	37	4	4	10
Reding et al., 1984	56	56	0	55	1	1	<2
Larson et al., 1985	200	200	0	198	2	2	1

*SOURCES: Listed in first column.

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, La Jolla
CA 92093

Table 5.—Disorders Producing Dementia: Diagnoses in Nine Clinical Series*

Diagnosis		N	Group	%
Alzheimer		499		
+ Parkinson		10		
+ Vascular		8		
TOTAL ALZHEIMER			517	65.9
Vascular (MID)[a]		85		
Parkinson		10		
Huntington		15		
PSP		3		
ALS		1		
Kufs		1		
Post-anoxic/CO		5		
Post-traumatic		8		
Post-encephalitic		3		
Creutzfeldt-Jakob		3		
TOTAL "OTHER IRREVERSIBLE"			134	17.1
Neurosyphilis		2		
Fungal infections		2		
Tumor		22		
Alcohol		22		
Subdural		4		
Hydrocephalus		27		
Epilepsy		3		
TOTAL "TREATABLE"			82	10.5
Drug toxicity		21		
Metabolic		16		
Hepatic	1			
Hyponatremia	1			
Calcium/PTH	4			
B-12	2			
Thyroid	7			
Hypoglycemia	1			
TOTAL "REVERSIBLE"			37	4.7
Cause uncertain		14	14	1.8
Total N		784	784	100

[a] Multi-infarct dementia.

*SOURCES: Series include Marsden and Harrison (1972), Freeman and Rudd (1982), Coblentz et al. (1973), Smith and Kiloh (1981), Rabins (1981), Delaney (1982), Garcia et al. (1981), and Larson et al. (1985).

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, La Jolla
CA 92093

Table 6.—Pathologgical Diagnoses in Dementia*

	< 70 Years of age		> 70 Years of age	
	N	%	N	%
Alzheimer atrophy	73	44.8	502	52.7
Vascular	25	15.4	214	22.5
Mixed Vasc/Alzheimer	1	0.6	148	15.2
Pick	15	9.2	8	0.8
Parkinson	3	1.8	10	1.0
Olivo-Ponto-Cerebellar	3	1.8	1	0.1
Wernicke encephalopathy	6	3.7	6	0.6
Post-anoxic	--		2	0.2
Post-traumatic	--		5	0.5
Hydrocephalus	9	5.5	5	0.5
Tumor	14	8.6	34	3.5
Creutzfeldt-Jakob	5	3.1	4	0.4
Inflammatory (MS/general paresis)	9	5.5	6	0.6
Unclassified or normal	--		8	0.8
Total N	163		953	

*SOURCE: From Jellinger (1976), Tomlinson (1977), and R. Terry (personal communication, 1985).

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD. La Jolla
CA 92093

Table 7.--Diagnostic Cerebral Biopsies

General series	Number of cases	Diagnostic	Abnormal but not diagnostic	Normal	Deaths	Morbidity
Antunes (1963)	28	15	6	7		
Eadie (1964)	50	15	14	21		
Blackwood & Cumings (1966)	178	77	66	35	0	0
Groves & Møller (1966)	117	44	37	36	1*	1**
Kaufman & Catalano (1979)	46	17	22	7	1'	5''
Total	419	168	145	106		
%		40	34.5	25.5		
Dementia series			No specific changes			
Green et al. (1952)	15	8	7		0	1``
Smith et al. (1966)	59	42	17		1`	0
Bowen et al. (1982)	36	28	8		---~~	---~~
Katzman et al.~ (update & series)	23	19	4		0	2
Total	133	97	36		1	3
%		73	27			

*Cardiac arrest, 15 months.
**Hemiparesis, cleared.
'Aspiration.
''3 pneumonia, 1 pulmonary embolus, 1 focal epilepsy.
`Subdural hematoma with pneumonia.
``Postoperative.
~Coblentz et al. (1973), Kaplan et al. (1985), Crystal et al. (1982), and Koto et al. (1977).
~~No report.

SOURCES: Listed in first column.

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, La Jolla
CA 92093

Table 8.--Comparison of Diagnostic Criteria--Alzheimer's and "Primary Degenerative Dementia" (PDD)

Criteria	DSM-III/ PPD	ADRDA/NINCDS Alzheimer's probable	ADRDA/NINCDS Alzheimer's possible	ADRDA/NINCDS Alzheimer's definite
Dementia present on:				
-clinical evaluation...	R	R	R	R
-mental status tests...		R	R	
Cognitive deficit in two or more areas......	R	R	+	
Impairment of function...	R	+	+	
Onset age 40 - 90.........		R	+	
Insidious onset...........	R	+	+	
Progressive course........	R	R*	R*	
Exclusive of systemic or brain disorders that may produce dementia................	R	R	+	
Exclusive of depression and other psychiatric disorders..............	R			
Tests:				
Normal LP...............		+	+	
EEG normal or slowing..		+	+	
CT atrophy..............		+	+	
Absence of focal motor or sensory changes.....		+	+	
Histological changes characteristic of Alzheimer's............				R

Note: R = required, + = desirable/not required.
*Accepts plateaus.

SOURCES: Amer. Psych. Assoc. Task Force (1980) and McKhann et al. (1984).

Robert Katzman, M.D.
Dept. of Neurosciences
UCSD, La Jolla
CA 92093

BASIC NEUROSCIENCE AND DISORDERS CAUSING DEMENTIA

Prepared for

The Office of Technology Assessment

of the Congress of the United States

by

Donald L. Price, M.D.
Neuropathology Laboratory
Departments of Pathology, Neurology, and Neuroscience
The Johns Hopkins University School of Medicine
509 Pathology Building
600 North Wolfe Street
Baltimore, Maryland 21205-2182
(301) 955-5632

February 1986

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS 4

INTRODUCTION 6

BASIC AND CLINICAL NEUROSCIENCE 9

STRUCTURE AND FUNCTION OF NORMAL NERVE CELLS 10

EFFECTS OF DISEASE ON NEURONS 14

ASSESSMENT OF BRAIN FUNCTION IN LIVING PATIENTS 16

NEUROSCIENCE: FUTURE DIRECTION AND BENEFITS 17

THE SYNDROME OF DEMENTIA 21

DEFINITION 21

MAGNITUDE OF THE PROBLEM 21

DISEASES ASSOCIATED WITH DEMENTIA 23

ALZHEIMER'S DISEASE 24

PARKINSON'S DISEASE 45

HUNTINGTON'S DISEASE 53

CREUTZFELDT-JAKOB DISEASE 59

ACQUIRED IMMUNE DEFICIENCY SYNDROME 66

CONCLUSION 77

ACKNOWLEDGEMENTS 79

LITERATURE CITED 80

FIGURES 137

(continued on next page)

Page

TABLES: I. DISORDERS CAUSING DEMENTIA.................................. 142

II. NEUROBIOLOGICAL APPROACHES.................................. 144

III. METHODOLOGIES OF POTENTIAL VALUE USED IN STUDIES OF HUMAN DEMENTIA OR IN STUDIES OF ANIMALS SHOWING CERTAIN FEATURES RESEMBLING THOSE IN HUMAN DISEASES.................. 146

APPENDICES: I. RECOMMENDATIONS FOR RESEARCH ON DEMENTIA................. 148

II. LETTER TO CONSULTANTS.................................. 152

III. LIST OF CONSULTANTS.................................. 153

IV. RESEARCH PROPOSALS: BACKGROUND, HYPOTHESIS, PREPARATION, REVIEW, AND FUNDING......................... 162

LIST OF ABBREVIATIONS

AChE	acetylcholinesterase
AD	Alzheimer's disease
AIDS	acquired immune deficiency syndrome
ARV	AIDS-associated retrovirus
cDNA	complementary deoxyribonucleic acid
ChAT	choline acetyltransferase
CJD	Creutzfeldt-Jakob disease
CNS	central nervous system
CRF	corticotropin-releasing factor
CSF	cerebrospinal fluid
EEG	electroencephalogram/graphic/graphy
GABA	gamma-aminobutyric acid
HD	Huntington's disease
HTLV-III	human T-cell leukemia (lympotropic) virus type III
kd	kilodaltons
LAV	lymphadenopathy-associated virus
MAP2	microtubule-associated protein 2
MPTP	1-methyl-4-phenyl-1,2,3,6,tetrahydropyridine
mRNA	messenger ribonucleic acid
NFT	neurofibrillary tangles
NIH	National Institutes of Health
PD	Parkinson's disease
PET	positron emission tomography
PHF	paired helical filaments

PRP	protease-resistant proteins
SDS	sodium docedyl sulfate
SNpc	substantia nigra, pars compacta

INTRODUCTION

The nervous system is, by several orders of magnitude, the most complex system in the biological world, and the functional activities of brain cells are the substrate of our intellectual and emotional lives. Unfortunately, these complex processes are easily perturbed by injury and disease. Among the most devastating human neurological disorders are a group of diseases affecting the parts of the brain responsible for cognition and memory. Dysfunction and death of nerve cells in these brain regions cause impairments in thought, memory, language, visuospatial skills, behavior, and personality. This constellation of symptoms and signs is termed "the syndrome of dementia". A variety of diseases can cause dementia, and these disorders are associated with a multiplicity of complex structural, chemical, and functional abnormalities involving different brain regions and different populations of nerve cells.

The goals of this review are to indicate, in substantial part by illustrative examples, how investigations of neuroscience have enhanced our understanding of these extraordinarily complex human disorders. It is not my purpose to review all of the clinical syndromes and causes of various types of dementia [Haase, 1977] (Table I). Instead, I have chosen to discuss five diseases -- Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Creutzfeldt-Jakob disease (CJD), and the acquired immune deficiency syndrome (AIDS) dementia complex -- as excellent examples of the ways in which concepts and multidisciplinary approaches of basic neuroscience (Tables II and III) have led to new insights into brain abnormalities associated with dementia. The major principle to be derived from this discussion is that understanding the extraordinarily complex disorders of the human mind will ultimately come from collaborative interactions of clinical and basic neuroscience and that these interactions must be encouraged at the highest level of our scientific and political leadership. The general organization of this review is outlined below.

- First, as background, I briefly review aspects of contemporary neuroscience, emphasizing new information derived from basic and clinical disciplines.
- Second, I define the syndrome of dementia and discuss the magnitude of this problem.
- Third, for each of the five diseases, I discuss:
    - clinical profiles of the illness;
    - laboratory studies, including recently developed technologies that have been used to clarify some of the brain abnormalities occurring in these patients;
    - exciting new investigations of structural and chemical brain abnormalities in individuals with different syndromes of dementia;
    - neurobiological investigations of animal models that clarify mechanisms of disorders occurring in human patients;
    - etiological factors important in the pathogeneses of human diseases; and

- the present status and future directions of treatment.

Review of these each of these issues provides many opportunities to demonstrate directly how approaches of basic and clinical neuroscience have provided new insights concerning the pathogeneses and potential treatments of these different types of dementia.

BASIC AND CLINICAL NEUROSCIENCE

During the past two decades, neuroscientists have clarified many fundamental issues concerning the biology of neurons and have delineated the anatomy, physiology, and chemistry of specific neuronal systems [Hubel, 1979; Hubel and Wiesel, 1979; Evarts, 1979; Iversen, 1979; Kandel, 1979; Nauta and Feirtag, 1979; Stevens, 1979; Abelson et al., 1985; Kandel and Schwartz, 1985b]. Moreover, new technologies derived from molecular and cellular biologies, genetics, immunology, biophysics, and computer science have allowed investigators to explore, in ways not previously possible, the structure and function of elements of the nervous system. Information from these approaches has been of great value to clinical neuroscience, which takes, as a starting point, problems encountered at the bedside and focuses on the causes, mechanisms, and treatments of diseases of the brain [Adams and Victor, 1985; Kandel and Schwartz, 1985b]. During the past decade, research in basic and clinical neuroscience has become increasingly interactive and multidisciplinary [Snyder, 1985b]. Complementary relationships between clinical and basic neuroscience are extraordinarily important because understanding various processes leading to dementia depends upon collaborative interactions between clinicians, neuropathologists, and basic neuroscientists. In these efforts, research must be broad based, because the directions leading to major advances are not necessarily predictable. As indicated by illustrations in this review, scientists from a variety of disciplines have used different approaches to advance our knowledge of diseases causing dementia.

STRUCTURE AND FUNCTION OF NORMAL NERVE CELLS

In the following section, I outline some of the recent advances in our current understanding of the structure and functions of nerve cells in the CNS (brain and spinal cord). Distinct types of neurons are located in different regions of the brain; these cells utilize specific neurotransmitters and make highly characteristic connections with other cell types. For heuristic purposes, I focus on: the regional specialization of neurons; protein synthesis and axonal transport; electrical and chemical signals; and chemical neuroanatomy.

Regional Specialization of Neurons

The brain is made up of billions of neurons, which come in all shapes and sizes. Individual neurons have unique geometries, and structural and chemical components of these cells and their relationships with each other have been delineated by a variety of morphological methods, including immunocytochemistry, Golgi preparations, autoradiography, and ultrastructural analyses [Peters et al., 1976; Hubel, 1979; Stevens, 1979; Hokfelt et al., 1985; Reichardt, 1985] (Fig. 1). Abundant evidence indicates that specific parts of cells have specific functional properties: the nucleus contains DNA and the elements necessary to transcribe DNA into RNA; the cell body (perikaryon) contains ribosomes that translate mRNAs into proteins, which are then subject to specific modifications (i.e., phosphorylation, cleavage, etc.); specialized transport systems deliver these proteins to axons and nerve terminals that lack the capacity for protein synthesis; the initial segment and nodes of Ranvier are specialized parts of the axonal membrane that generate and conduct action potentials; and, at synapses (points of contact between nerve cells), the presynaptic terminal contains neurotransmitter molecules (e.g., acetylcholine, norepinephrine, somatostatin, etc.) in membranous packages (vesicles), and, when the terminal is depolarized, these substances are released at specific sites (active zones) located directly adjacent to receptor-rich postsynaptic membranes of target cells. Investigations during the past decade have demonstrated that many neurological disorders are associated with involvement of specific neuronal populations and with abnormalities of specific processes within nerve cells.

Protein Synthesis and Axonal Transport

The complex geometries of neurons require specialized internal communication systems to deliver materials to different parts of individual nerve cells. The perikaryon is the principal site of protein synthesis, and axons and nerve terminals depend on this source for a continual supply of proteins. These axonal transport systems are distinguished on the basis of direction and rate of movement into fast, slow, and intermediate anterograde transports (carrying materials away from the cell body) and retrograde transport (carrying materials toward the cell body). Proteins can be labeled by injecting radioactive amino acids in proximity to nerve cell bodies, and distributions of labeled proteins can be examined using autoradiography, radiometric methods, and gel fluorography. These approaches have identified some of the transported proteins and related these proteins to specific organelles within nerve cells. For example, neurofilament proteins (200, 145, and 68 kd) [Hoffman and Lasek, 1975], which are, along with tubulin and actin, the major components of the neuronal cytoskeleton, are transported slowly anterograde as formed neurofilaments. In axons, neurofilaments play a major role in determining axonal caliber [Hoffman et al., 1985a,b] and caliber-dependent physiological properties of axons (e.g., conduction velocity of the action potential, degree of myelination, etc.). Moreover, elements of the cytoskeleton play key roles in intracellular communication, and research on the molecular basis of transport of specific constituents in cells is one of the most active areas of contemporary neuroscience [Schnapp et al., 1985; Vale et al., 1985a,b,c].

Perturbations of these transport systems, including the neuronal cytoskeleton, have profound effects on the structure and function of neurons. Indeed, current evidence suggests that disturbances of the neuronal cytoskeleton occur in several major human diseases, including AD [Price, 1986; Price et al., 1986], PD [Goldman, 1983], and amyotrophic lateral sclerosis [Griffin et al., 1983; Price et al., 1984]. In addition, transmitter-synthesizing enzymes (e.g., ChAT) and neuropeptides (e.g., somatostatin, CRF, etc.) are manufactured in neuronal perikarya and delivered by axonal transport to nerve terminals, where they play essential roles in synaptic transmission. Recent observations suggest that neurons that appear unremarkable in conventionally stained preparations may not have a normal content of transmitter-specific constituents. For example, in monkeys intoxicated with MPTP, dopaminergic neurons in the SNpc show reduced levels of tyrosine hydroxylase [Kitt et al., in press], an enzyme important in the synthesis of dopamine. Similar processes, involving transmitter-specific properties of neurons, may occur in human disorders.

Electrical and Chemical Signals

Neurons communicate by electrical and chemical (neurotransmitter) signals. When a nerve cell is excited by incoming synaptic inputs, the initial segment (the part of the axon adjacent to the perikaryon), is depolarized, and an action potential is generated and propagates rapidly down the axon [Stevens, 1979,1985; Catterall, 1985]. When the action potential invades and depolarizes synaptic nerve terminals, Ca^{++} permeability is increased at the terminal, and neurotransmitter-laden vesicles fuse with the presynaptic membrane at active zones. The transmitter molecule, released by exocytosis, diffuses across the synaptic cleft and interacts with receptors concentrated on the membrane of the postsynaptic cell. This interaction of transmitter molecules with receptors initiates changes in conductance/resistance of postsynaptic membranes and, depending on the character of these events, the cell may be excited, inhibited, or modulated (in some instances, by a second messenger) [Schramm and Selinger, 1985]. Signal transduction may be mediated by several chemical mechanisms, including phosphorylation of specific proteins and turnover of inositol phospholipids [Nestler et al., 1985; Nishizuka, 1985]. It is likely that alterations in these processes may occur in certain neurological disease in humans. In addition to these electrical and transmitter signals, certain populations of neurons are also strongly influenced by nontransmitter chemical mediators, i.e., trophic or growth factors [Levi-Montalcini and Angeletti, 1968; Thoenen and Barde, 1980; Barde et al., 1983]. Reciprocal influences between neurons and targets may underlie extremely important biological functions of neurons. Deficiencies of trophic factors may play roles in the pathogeneses of degenerative disorders of the nervous system [Appel, 1981].

Chemical Neuroanatomy

Our knowledge of the anatomical-chemical organization of the brain has been enormously enhanced by the development and application of a variety of new technologies, e.g., immunocytochemistry, in situ hybridization, receptor binding studies, neurochemical analyses, and radioimmunoassays. These approaches have allowed identification of specific populations of neurons that use different transmitters (including acetylcholine, catecholamines, excitatory amino acids, and peptides) and express a variety of receptors [Emson, 1983; Changeux et al., 1985; Hokfelt et al., 1985; Snyder, 1985a; Whitehouse, 1985; Kuhar et al., 1986], which are the targets of psychoactive drugs. Moreover, multidisciplinary approaches have begun to define the connectivities, physiological properties, and influence of targets of neurons in these systems. Some of the results of these investigations, particularly of cholinergic and peptidergic systems in brain, have led to new insights into neurotransmitter abnormalities occurring in AD, PD, and HD (see discussions of specific diseases).

EFFECTS OF DISEASE ON NEURONS

Significant progress has been made in understanding the ways in which brain cells are affected in several types of dementia and in experimental disorders that reproduce aspects of the human disease. The selective effect of disease on specific neurons and on specific structural and functional properties of these neurons is termed "selective vulnerability" [Price and Griffin, 1980]. Different clinical syndromes result from selective effects of disease on different types of neurons in different regions of brain. For example, HD selectively involves certain populations of neurons (cholinergic and GABAergic cells in the striatum), and the wild, choreoform movements occurring in these patients are attributed to these lesions [Martin, 1984; Price et al., 1986]. In some instances, aspects of some of these pathological processes can be reproduced in animal models. The MPTP model of PD is a good example of an animal disorder that shows remarkable similarities to the human condition.

In these models, it is possible to examine, using new technologies, dynamic alterations in normal biological mechanisms. Strategies are now available to delineate, in affected neurons, structural, chemical, and functional changes at multiple levels: genetic abnormalities; alterations in gene expression; changes in mRNA processing; abnormalities in the synthesis and posttranslational modification of proteins; levels of specific proteins (e.g., transmitter enzymes); altered properties of specific molecules; impaired axonal transport of proteins (e.g., neurofilaments); and altered electrical properties and synaptic interactions of neuronal systems. Moreover, in the future, it should be possible to clarify the roles of specific neuronal populations on processes underlying complex neural activities associated with memory, cognition, behavior, etc., and to delineate the consequences of lesions of these cells on cognition and other functions. Finally, neurobiological investigations of experimental disorders will provide new insights into the mechanisms of neuronal death [Hamburger and Oppenheim, 1982; Horvitz et al., 1982; Truman and Schwartz, 1982], plasticity [Black et al., 1985; Cotman and Nieto-Sampedro, 1985], and regeneration-repair [Aguayo et al., 1982; Björklund et al., 1983; Dunnett et al., 1983; Gage et al., 1983; Price et al., 1984; Gash et al., 1985; Hoffman et al., 1985b]. These studies are essential if we are to understand the causes, mechanisms, and consequences of brain abnormalities leading to dementia and if we are to devise new treatments for these disorders.

ASSESSMENT OF BRAIN FUNCTION IN LIVING PATIENTS

During the past decade, substantial progress has been made in the development and application of clinical and laboratory methods for the assessment of brain function in individuals with various types of dementia [McKhann et al., 1984]. Clinical criteria for the diagnosis of some of these types of dementia have been refined [McKhann et al., 1984]. Certain laboratory studies have particular value in the evaluation of certain types of dementia. The EEG allows analysis of brain electrical activity, and evoked potentials are brain waves associated with sensory or other events. In AD, EEGs often demonstrate increased slow-wave activity that may become more pronounced with progression of the disease, and evoked potentials (such as P300, which reflects speed of cognition) may have an increased latency. Computerized tomography allows visualization of gyri and sulci and can be used to assess tissue densities, ventricular size, CSF volume, and brain mass. In the evaluation of demented individuals, this technique is very useful because it may detect potentially treatable disorders, e.g., subdural hematoma, brain tumor, etc., which may mimic types of dementia for which we do not have effective therapies. Magnetic resonance imaging is a technique that permits higher resolution than computerized tomography and allows demarcation of grey and white matter; this imaging method should prove useful in differentiating multi-infarct dementia and AD and has recently been useful in delineating white matter lesions in AIDS encephalopathy. Regional cerebral blood flow, which can be measured with [133]Xenon clearance and other techniques [Friedland et al., 1984; Frackowiak and Gibbs, in press], can also help separate patients with multi-infarct dementia from those with AD. Finally, PET allows quantitative analyses of glucose utilization, oxygen consumption, regional cerebral blood flow, and, in more recent investigations, localization and levels of transmitter-related markers. As such, PET will undoubtedly contribute substantially to our understanding of cerebral function and hemispheric specialization in normal individuals and in patients with neuropsychiatric disease [Mazziotta and Phelps, 1985]. For example, patients with AD show cerebral hypometabolism, particularly in parietal and temporal regions [Friedland et al., 1983], a change that correlates with impairments on neuropsychological test performance [Foster et al., 1983; Haxby et al., 1985], while, early in the course of disease, patients with HD have reduced glucose utilization in the striatum [Kuhl et al., 1985a]. During the next decade, radiochemists will undoubtedly develop a wide variety of labeled pre-and postsynaptic markers for delineating transmitter systems, as has recently been achieved for the dopamine and opiate systems. Using these new techniques, studies may be very useful in diagnostic evaluations, staging of disease, documenting progression, and assessing effects of treatment. However, the most important area of laboratory research relative to the problem of dementia is the development of new techniques to establish accurate premortem diagnoses by demonstration of the presence of specific biological markers in individuals with each disease. Accuracy of diagnosis is an extremely important issue in the evaluation of dementia for many reasons but particularly for designing and evaluating treatments for specific disorders.

NEUROSCIENCE: FUTURE DIRECTION AND BENEFITS

Understanding the complexities of the nervous system in health and disease is one of the greatest intellectual challenges facing mankind, and it seems that neuroscience will be the most exciting area of research in the next century. In spite of recent reductions in federal funding, an increasing number of investigators, including some of the outstanding early contributors to the field of molecular biology, are making career commitments to research on the nervous system. Many of the brightest students in our undergraduate and graduate schools elect additional training in neuroscience because they recognize that research on the brain represents the next great frontier in science and has the potential for great social benefit. Evidence of the growth and interest in neuroscience is reflected by growth of the Society for Neuroscience, which now has approximately 10,000 members.

At present, research in neuroscience has great momentum, and information derived from new technologies will provide extraordinary opportunities for understanding brain structure and function in health and disease. For example, molecular biologists are actively cloning many genes coding for mRNAs of proteins important in neural function. A variety of probes (e.g., cDNA probes, riboprobes, synthetic oligonucleotides probes) allow studies of mRNA levels in normal brain and in disease. Moreover, techniques of molecular biology can be used to study the character of specific genes and factors controlling gene expression. Eventually, these genes and their products will have to be understood in the context of biological properties of brain cells. This information should be extraordinarily valuable for our thinking about disease processes. Consider how these approaches can provide information about two diseases. In HD, a gene abnormality has been localized to chromosome 4 [Gusella et al., 1983]. This is certainly a great advance, but the gene and its translation product now need to be identified and the biological function (and location) of this protein determined in normal brain. With this information, we will be in a better position to learn how a genetic abnormality leads to cellular abnormalities in the striatum. In AD, abundant evidence indicates that, at one level, this disorder profoundly alters the cytoskeleton of neurons in certain populations. Some affected individuals with AD appear to have inherited the disease as an autosomal dominant. Techniques of molecular biology should eventually allow investigations designed to clarify, at a molecular level, the genetic basis of disturbances of the cytoskeleton in AD. Investigations of these types will certainly lead to new understanding of the cellular bases of cognition, learning, memory, emotion, etc., in man, and this information will be extraordinarily valuable for designing investigations intended to clarify mechanisms leading to the different types of dementia occurring in humans.

The problem of dementia is an extraordinarily complex one, resulting from multiple pathological processes involving different parts of the brain/neuronal systems, and it will not be understood using a single approach. A broad-based approach is necessary and requires a major commitment of resources to neuroscience. Information from these investigations will provide new insights into major human diseases, including the dementias, and should also serve to clarify our thinking about a variety of other neuropsychiatric disorders, including manic depressive psychosis and schizophrenia. More generally, neuroscience will provide new understanding about the brain -- the organ with which we view ourselves. At present, neuroscience is in a position analogous to that, at earlier times, of particle physics, molecular biology, cancer research, and space exploration. Only by substantial allocation of resources to basic and clinical research, particularly to multidisciplinary studies implemented by interacting clinical and basic science, will we be in a position to understand and treat disorders of the human mind.

THE SYNDROME OF DEMENTIA

DEFINITION

Dementia is the syndrome (i.e., symptom complex) characterized by decline of memory and other cognitive functions as compared to the patient's previous level of performance [Wells, 1977; McKhann et al., 1984]. Usually, the most conspicuous symptom is loss of memory, but patients also develop impairments of thought, language, calculation, visuospatial perception, judgment, behavior, etc. Dementia can be caused by a variety of disorders of different etiologies (Table I), and the character of the clinical course of dementia varies with the underlying nature of the illness [Haase, 1977; Adams and Victor, 1985]. Depending on the disease, the clinical syndrome may be associated with other neurological symptoms and signs and with specific abnormalities detected by laboratory studies.

MAGNITUDE OF THE PROBLEM

Dementia can occur in early adult life, as occurs in individuals with HD, with Down's syndrome (associated with AD-type pathology), or with AIDS. At age 65, approximately 10-15% of individuals exhibit symptoms of dementia, and this syndrome is the major reason for confinement of elderly individuals to nursing homes. An even greater percentage of individuals over the age of 85 develop dementia. The most common types of dementia occurring in these older individuals are AD and PD; it is estimated that perhaps 2.5 million demented individuals suffer from these two disorders. Demographic studies indicate that our aged population is rapidly increasing and that the frequency of AD and PD will increase as our population ages [Report of the Secretary's Task Force on Alzheimer's Disease, 1984]. For example, in the United States in 1900, there were approximately 3.1 million people over the age of 65; in 1980, this figure reached 26 million and will reach approximately 35 million (13% of the total population) by the year 2000. By the time individuals born during the immediate post-World War II period reach the age of 65 (year 2025), some 60 million individuals (20% of the population) will be in the high-risk group. In the United States today, the cost of nursing home care for elderly demented patients exceeds $20 billion dollars annually, imposing substantial personal and economic burdens on families and on society. Without research to provide new information about the ways to deal with these diseases, all of us will soon be confronted with the enormous problem of providing care for the many individuals with untreatable types of dementia.

DISEASES ASSOCIATED WITH DEMENTIA

The syndrome of dementia may be associated with a variety of disorders [Haase, 1977] (Table I). The most common type of dementia, particularly of those occurring in the elderly, is AD, a complex disease involving several populations of nerve cells in several regions of brain [Terry and Katzman, 1983; Price et al., 1985c; Price, 1986; Price et al., 1986]. In this age group, a significant number of patients may also have cognitive impairments due to hypoxic-ischemic brain damage or to cerebrovascular disease (stroke), a syndrome termed multi-infarct dementia. Because older individuals are prone to both vascular disease and AD, some patients have a mixed type of dementia, with both pathological processes contributing to the clinical manifestations of disease. Another common cause of dementia in older individuals is PD; approximately 40% of the 500,000 individuals with PD develop moderate-to-marked dementia [Lieberman et al., 1979; Boller et al., 1980; Mayeux et al., 1981]. Some of these individuals have brain abnormalities resembling those occurring in AD, while other patients do not have AD-type pathology [Hakim and Mathieson, 1979; Boller et al., 1980; Perry et al., 1983; Ball, 1984; Price et al., 1986; Quinn et al., in press]. Occurring in mid-adult life, HD is an autosomal dominant disorder [Gusella et al., 1985] characterized by involuntary movements (chorea) and cognitive and behavioral abnormalities [Martin, 1984]. CJD is a rare type of adult-onset dementia [Gajdusek, 1984b,1985b] caused by an unusual transmissible agent (thought to be an unconventional virus). Finally, an increasingly common cause of dementia in young adults is AIDS [Nielsen et al., 1984; Epstein et al., 1985b; Shaw et al., 1985; Navia et al., in press a,b;

Price et al., in press b], a disease caused by a retrovirus infection occurring in certain high-risk groups of patients. In each of these disorders, substantial progress has been made in understanding the brain abnormalities underlying the clinical syndromes, and selected aspects of investigations of these disorders are reviewed below.

ALZHEIMER'S DISEASE

Clinical Manifestations

Occurring in middle or late life, AD is characterized by insidiously appearing impairments in memory and cognition. Criteria for a clinical diagnosis of AD have recently been reviewed by a joint work group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [McKhann et al., 1984]. Affected individuals frequently exhibit disorders of language, calculation, visuospatial perceptions, judgment, behavior, etc., and some patients develop psychiatric symptoms, including depression and hallucinations. Fluctuations in task performance may occur in individual patients, but, more commonly, mental functions and activities of daily living become progressively more impaired. The observation that AD is associated with different clinical syndromes has led some investigators to suggest that there may exist subtypes of AD, i.e., early vs. late onset, familial vs. sporadic; benign vs. malignant, etc. [Sjogren et al., 1952; Roth, 1978; Folstein and Breitner, 1981; Seltzer and Sherwin, 1983; Jorm, 1985; Mayeux et al., 1985]. In later stages of disease, however, virtually all patients are profoundly demented, mute, incontinent, and bedridden. Life expectancy is shortened. Although these patients die of intercurrent illnesses (e.g., pneumonia, pulmonary embolism, etc.), the true cause of death is AD.

Laboratory Studies

Unfortunately, at present, there are no laboratory tests that permit clinicians to establish an unequivocal diagnosis of AD [McKhann et al., 1984]. A diagnosis of AD can be suspected on the basis of clinical criteria but can only be established by a biopsy or by postmortem examination of brain. However, the accuracy of diagnosis in a clinical setting is increased by laboratory examinations (e.g., computerized tomography, CSF examination, etc.) that demonstrate other causes of dementia (e.g., subdural hematoma, intracranial tumor, infection, brain infarction, etc.). In AD, several investigative approaches show patterns consistent with, but not diagnostic of, the disease [McKhann et al., 1984]. EEGs commonly detect diffuse slow-wave activity over the hemisphere. Evoked potentials frequently have increased latencies as compared to age-matched controls. Computerized tomography helps to exclude other diagnoses and, in AD, commonly demonstrates the volume of the ventricular system, the width of the third ventricle, narrowing of gyri, and widening of sulci [Gado et al., 1983]. Although it is too early to fully evaluate the efficacy of magnetic resonance imaging for evaluating patients with AD, it is likely that the higher resolution of this technique will be most useful in excluding certain other types of dementia, particularly multi-infarct dementia, which can mimic AD. Dynamic imaging studies of patients with AD have demonstrated reductions in regional cerebral blood flow, oxygen consumption, glucose metabolism, and protein synthesis [Ingvar and Lassen, 1979; Bustany et al., 1983; Friedland et al., 1983; Frackowiak and Gibbs, 1983; Foster et al., 1984; Haxby et al., 1985; Kuhl et al., 1985b; Frackowiak, in press], and correlations have been demonstrated between results of these imaging studies and the character of neuropsychological deficits. For example, patients with language impairments exhibit reduced metabolic activity in the left parietal-temporal region, while individuals with visuospatial problems show alterations in corresponding areas of the right hemisphere [Foster et al., 1984]. Unfortunately, changes in patterns of brain metabolism are not specific for AD. The development of new markers for transmitter systems should lead to investigations that should provide more specific information about alterations in neuronal circuits in AD.

Brain Abnormalities

Studies defining the chemical neuroanatomy of specific systems and delineating the biology of the neuronal cytoskeleton are of particular relevance to investigations of the structural and chemical pathology of AD. AD selectively affects certain groups of neurons in specific regions of brain, including cells in the basal forebrain (cholinergic system), in certain brainstem nuclei (locus coeruleus and raphe complex), and in the amygdala, hippocampus, and neocortex. Affected neurons develop structural pathology, including NFT in perikarya and neurites in senile plaques; some neurons contain Hirano bodies and granulovacuolar pathology. Current evidence suggests that each of these abnormalities are cytological expressions of alterations in the neuronal cytoskeleton. The presence of structural pathology in neurons indicates that affected cells are not functioning normally, but we have little information about the causes, mechanisms, and time courses of these processes. Eventually, affected nerve cells degenerate.

Neurofibrillary Tangles

NFT, filamentous inclusions in the cell bodies of nerve cells, occur in amygdala, hippocampus, basal forebrain cholinergic system, certain monoamine nuclei of the brainstem, and in association cortices of the frontal, parietal, and temporal lobes. In cortex, NFT are usually most conspicuous in supra- and infragranular layers (III and V) and often appear to be arranged in clusters, a pattern that has been interpreted to suggest that processes leading to the formation of NFT may involve anatomical pathways [Pearson et al., 1985]. NFT-containing neurons eventually die, leaving behind extracellular accumulations of filaments [Probst et al., 1982; Saper et al., 1985]. The presence of cortical NFT correlates with the presence of dementia [Wilcock and Esiri, 1982].

Electron microscopy has demonstrated that NFT are composed of accumulations of paired filaments (e.g., PHF), which are made up of 8-12 nm filaments crossing over every 80 nm [Kidd, 1963; Wisniewski et al., 1976,1984]. PHF are frequently associated with 15-nm straight filaments and 10-nm neurofilaments, and these different types of filaments may represent stages in the evolution of pathology. Some immunocytochemical studies suggest that neurofilaments, particularly phosphorylated epitopes of the 200-kd neurofilament protein, and microtubule-associated proteins (e.g., MAP2 and tau) are either intimately associated with, or are components of, PHF [Anderton et al., 1982; Gambetti et al., 1983; Kosik et al., 1984; Rasool and Selkoe, 1984; Perry et al., 1985;

Sternberger et al., 1985; Cork et al., 1986; Kosik et al., in press]. The formation of PHF may bury some epitopes and create new antigenic determinants [Ihara et al., 1983; Rasool and Selkoe, 1984; Rasool et al., 1984; Yen et al., 1985]. Ultrastructural images of PHF are not consistent with the concept that these filaments are simply a modification of normal neurofilaments [Wisniewski et al., 1984; Wischik et al., 1985]. Biochemical studies have show that PHF are protein polymers that are difficult to solubilize using conventional techniques [Selkoe et al., 1982], making it difficult to determine the composition of PHF. However, recently, PHF appear to have been solubilized using high concentrations of formic acid [Masters et al., in press; Selkoe, in press; Selkoe and Abraham, submitted for publication], and current evidence suggests that PHF may have, as a major protein component, a 4-kd monomer that can form dimers, tetramers, and hexadecamers [Masters et al., in press]. Moreover, as described below, similar proteins appear to be present in the amyloid of plaque cores and in the amyloid of congophilic angiopathy [Masters et al., 1985]. Finally, NFT-bearing neurons appear to be enriched in aluminum [Perl and Brody, 1980].

Senile Plaques

These spherical foci (up to 200 μm in diameter) are made up of enlarged filament-containing axons/synaptic terminals/dendrites (neurites) associated with extracellular amyloid [Kidd, 1964; Gonatas et al., 1967; Wisniewski and Terry, 1973; Gonatas and Gambetti, 1980; Probst et al., 1983; Perry and Perry, 1985]. Thought to represent sites of abnormal synaptic interactions [Gonatas et al., 1967], plaques occur in high frequency in amygdala, hippocampus, and neocortex [Jamada and Mehrsein, 1968; Kemper, 1983; Pearson et al., 1985]. In cortex, plaques occur in all layers but are particularly frequent in layers II and III [Pearson et al., 1985]. In contrast to NFT, plaques usually do not cluster [Pearson et al., 1985]. In AD and in aged primates, neurites in plaques are derived from a variety of transmitter systems, including cholinergic, catecholaminergic, and peptidergic neurons [Kitt et al., 1984,1985; Struble et al., 1984b,1985a; Morrison et al., 1985; Walker et al., 1985; Powers et al., in press]. Many neurites appear to be degenerating neuronal elements, and some could represent regenerating axonal processes [Gonatas and Gambetti, 1980; Price, 1986]. The presence of plaques correlates with reductions in cholinergic and somatostatinergic markers [Perry et al., 1978] and with the presence of dementia [Tomlinson et al., 1970].

In AD, neurites in plaques contain a mixture of PHF, 15-nm straight filaments, and neurofilaments, while, in aged monkeys, neurites in plaques predominantly contain neurofilaments -- an observation that suggests that PHF are not necessary for the formation of neurites. Relationships between filaments in neurites and fibrils of amyloid are not yet clear. Amyloid fibrils are made up of proteins arranged in a predominantly β-pleated sheet configuration. Some investigators believe that degenerating fibrillary components of neurons (e.g., neurites or NFT) may give rise to plaque amyloid [Powers et al., 1981; Price et al., 1982; Masters et al., in press], while other investigators suggest that serum proteins pass through the blood-brain barrier, are locally deposited (in perivascular regions and neural parenchyma), and act to injure neuronal processes [Glenner, 1983a,b]. Relatively purified preparations of plaque cores from individuals with AD and from an aged individual with Down's syndrome contain multimeric aggregates of a 4-kd monomer [Masters et al., 1985], and the amino acid composition, molecular mass, and NH2 terminal sequence of this protein are almost identical to those described for the amyloid deposited in congophilic angiopathy [Glenner and Wong, 1984]. Sequences of these proteins are different from any sequences of catalogued naturally occurring proteins and from the amyloid proteins appearing in scrapie-infected brain [Prusiner et al., 1984].

Preliminary studies using antisera raised against synthetic peptides indicate that the N terminus of A4 (residues 1-11) contains an epitope present in NFT, while residues 11-23 contain an epitope expressed in plaque cores and vascular amyloid [Masters et al., in press]. These results suggest that NFT, plaque cores, and cerebrovascular amyloid share antigenic determinants. It has been speculated that abnormal filaments are formed first within neurons, and, as neuronal elements degenerate, abnormal proteins are liberated into the microenvironment of the neuropil where they are, in ways yet unclear, are converted into plaque amyloid and, at a later stage, into vascular amyloid.

A variety of approaches, including energy-dispersive x-ray analysis, have demonstrated the presence of aluminum and silicon in plaque cores [Duckett and Galle, 1976; Perry and Perry, 1985]. It is not clear how these deposits are related to the presence of amyloid proteins.

Hirano Bodies

Common in the pyramidal cell layer of hippocampi in patients with AD [Gibson and Tomlinson, 1977], these rod-shaped cytoplasmic inclusions are comprised of thin filaments that show actin-like immunoreactivity [Goldman, 1983]. In freeze-fracture/deep-etch images, Hirano bodies appear as paracrystalline arrays of actin (J. Heuser and D.L. Price, personal observation).

Granulovacuolar Degeneration

These single, electron-dense granules, each within a membrane-limited vacuole, are frequent in the cytoplasm of pyramidal neurons in hippocampi of individuals with AD [Tomlinson and Kitchener, 1972; Ball, 1977]. Immunocytochemical studies suggest that these granules are enriched in tubulin-like immunoreactivity [Price et al., 1985b]. Indirect evidence suggest that the formation of these granules in pyramidal neurons of the hippocampus is eventually associated with death of these cells.

Affected Neuronal Systems

The structural pathology described above occurs in specific neuronal systems, and alterations of these neurons are associated with abnormalities of transmitter-specific circuits.

Basal Forebrain Cholinergic System

To date, the most consistently affected transmitter system in brains of individuals with AD is the basal forebrain system, which provides the principal cholinergic innervation of amygdala, hippocampus, and neocortex [Mesulam et al., 1983; Hedreen et al., 1984; Struble et al., in press a,b]. Studies of biopsies of cortex from younger patients with AD suggest that reductions in the synthesis of acetylcholine occur early in the course of disease and that these deficits correlate with cognitive impairments [Francis et al., 1985]. In AD, cholinergic neurons in the medial septum, diagonal band, and nucleus basalis develop NFT

[Saper et al., 1985], and evidence from studies of aged monkeys suggests that distal axons/nerve terminals of these cells can form neurites in some senile plaques [Struble et al., 1982,1984b; Price et al., 1983; Kitt et al., 1984]. As these nerve cells degenerate [Whitehouse et al., 1982; Arendt et al., 1983; Candy et al., 1983; Saper et al., 1985], cholinergic markers (including nicotinic receptors and presynaptic M2 receptors) are reduced in amygdala, hippocampus, and neocortex [Davies and Maloney, 1976; Bowen et al., 1976; Sims et al., 1983; Mash et al., 1985; Whitehouse et al., in press a,b].

Brainstem Monoamine Systems

In some patients, neurons in the locus coeruleus show NFT, and their axons/terminals form noradrenergic neurites in senile plaques [Powers et al., in press]. Neurons in the locus coeruleus are reduced in number, and noradrenergic markers are decreased in cortex [Adolfsson et al., 1978; Cross et al., 1981; Perry et al., 1981; Tomlinson et al., 1981; Bondareff et al., 1982; Iversen et al., 1983; Yates et al., 1983]. Serotonergic neurons of the raphe complex show NFT and are reduced in number [Curcio and Kemper, 1984; Yamamoto and Hirano, 1985]; changes also occur in serotonergic markers, including uptake of [^{3}H] serotonin, binding of [^{3}H] imiprimine, endolamine content [Bowen et al., 1983], and reduced numbers of S2 receptors [Perry et al., 1984; Reynolds et al., 1984].

Amygdala

NFT, senile plaques, and neuronal loss occur in the amygdala [Jamada and Mehraein, 1968; Herzog and Kemper, 1980]. Central and medial nuclei show the greatest neuronal loss, while the basolateral complex, which is related to limbic and association neocortices, shows high densities of NFT and senile plaques [Kemper, 1983].

Hippocampus and Associated Circuits

Hippocampal pyramidal neurons commonly develop NFT and frequently also contain Hirano bodies, granulovacuolar degeneration, and changes in dendritic geometries [Hirano and Zimmerman, 1962; Tomlinson and Kitchener, 1972; Ball, 1977; Gibson and Tomlinson, 1977; Ball, 1978; Buell and Coleman, 1981; Probst et al., 1983; Ball et al., 1985]. Neurons in the subiculum and in layers II and IV of entorhinal cortex also develop NFT and altered dendritic arbors [Buell and Coleman, 1981]; these lesions may serve to isolate the hippocampal formation from association cortex and other structures important in memory [Kemper, 1978; Hyman et al., 1984]. Excitatory amino acids may be important transmitters in some of these circuits. Plaques are common in hippocampus and in medial temporal cortex, and neurites in plaques are derived from a variety of transmitter systems [Struble et al., 1985a; Powers et al., in press]. Deafferentation of hippocampus may be associated with sprouting of axons of several fiber systems [Geddes et al., in press]. These findings are consistent with the idea that some neurites may represent abortive regenerates [Gonatas and Gambetti, 1970; Price et al., 1983; Price, 1986].

Neocortex

NFT, plaques, and reductions in numbers of neurons are consistently demonstrated in cortex [Colon, 1973; Shefer, 1973; Terry, 1981; Mountjoy et al., 1983; Mann et al., 1985; Pearson et al., 1985]. Somatostatinergic neurites develop NFT [Roberts et al., 1985], and, in individuals with AD and in aged primates, processes of these cells form neurites in plaques [Struble et al., 1984b; Morrison et al., 1985]. Levels of somatostatin-like immunoreactivity are reduced [Davies et al., 1980; Rossor et al., 1980; Ferrier et al., 1983], and the number of somatostatin receptors is decreased [Beal et al., 1985]. Levels of immunoreactivity of CRF, a neuropeptide present in some cortical neurons and in brainstem neurons projecting to cortex, are decreased [Bissette et al., 1985b; DeSouza et al., 1986], and there is a reciprocal increase in CRF receptors [DeSouza et al., 1986]. It is difficult to visualize cortical CRF neurons using immunocytochemistry in autopsy material; perhaps these cells can be identified by *in situ* hybridization using labeled synthetic probes that detect CRF mRNAs. A variety of other peptidergic systems (e.g., those using vasoactive intestinal peptide, cholecystokinin, etc.) appear relatively spared [Rossor et al., 1982; Ferrier et al., 1983]. However, some of these peptidergic systems, which do not show reductions by radioimmunoassay, do contribute neurites to plaques [Struble et al., 1985b]. For other affected neuronal populations, transmitters have not yet been established, but it is likely that some affected pyramidal neurons in cortex use excitatory amino acids as transmitters. At present, we do not have good morphological markers for these cells, and reliable chemical assays for these systems are not available. Studies of receptors in cortex have demonstrated reductions in cholinergic, nicotinic, somatostatinergic, and glutamate receptors [Beal et al., 1985; Greenamyre et al., 1985; Mash et al., 1985; Whitehouse et al., in press a,b], and, as mentioned, increases in CRF receptors [DeSouza et al., 1986].

Clinicopathological Correlations

Because AD involves a variety of regions of brain and a variety of transmitter systems, it is difficult to make clinicopathological correlations; however, extrapolations of the consequences of other types of lesions in experimental animals and in humans have provided some clues to the pathological substrate of aspects of this clinical syndrome. Impairments in memory may result, in part, from a combination of lesions: deafferentation of amygdala and hippocampus; pathology intrinsic to hippocampus; and abnormalities of circuits linking hippocampus to neocortex. Abnormalities in amygdala may contribute to some behavioral problems occurring in these patients. Focal cortical signs (e.g., language abnormalities, visuospatial impairments, etc.) may be attributed to deafferentation of specific neocortical regions by lesions of certain corticopetal brainstem and basal forebrain systems admixed with pathology involving neurons intrinsic to neocortex. For example, language abnormalities may be associated with reductions in subcortical-cortical cholinergic and catecholaminergic inputs to the left parasylvian region in combination with abnormalities of intrinsic neurons (e.g., those using somatostatin, CRF, or excitatory amino acids as transmitters). The global dementia and diffuse reductions in electrical activity and metabolism occurring in later stages of disease are believed to reflect bilateral distributions of these processes.

Animal Models

At present, there exists no satisfactory model for AD. Some older macaques show age-associated cognitive deficits [Bartus et al., 1978; Davis, 1978; Struble et al., 1985c] and senile plaques [Wisniewski et al., 1973; Struble et al., 1982,1984a], but, to our knowledge, these animals do not develop AD [Price et al., 1985a]. Similarly, certain strains of mice infected with scrapie develop senile plaques [Wisniewski et al., 1975; Dickenson et al., 1983], but little information is available about the behavior of these animals. For purposes of discussion, we focus on two primate models that have proved useful for exploring certain processes similar to those occurring in AD.

Cholinergic Deficiency in Amygdala, Hippocampus, and Neocortex

When neurons in the basal forebrain cholinergic system are selectively destroyed bilaterally in monkeys, ChAT activity in amygdala, hippocampus, and neocortex is reduced in parallel with the location and extent of the lesion [Struble et al., in press a,b]. Animals who have bilateral partial lesions of the nucleus basalis do not show overt impairments on memory tasks, but their performance on these tasks is sensitive to scopolamine [Aigner et al., 1983]. When these bilateral lesions are more extensive, e.g., involving the medial septum, diagonal band, and nucleus basalis, animals have some impairment in recognition memory [Aigner et al., 1984]. It is of interest that AChE preparations in some lesioned animals disclosed axons with unusual shapes; some of these enlarged axons resembled neurites in plaques. It is possible that these axons represent sprouts participating in a regenerative response to cholinergic deafferentation of target fields. These observations of altered behavior in lesioned animals are consistent with the concept that lesions of the basal forebrain cholinergic system may be associated with memory deficits. Similar strategies can be used to damage other neuronal systems (e.g., noradrenergic neurons, somatostatinergic neurons, etc.) and then to assess the effects of these lesions on behaving animals. This approach may serve to clarify behavioral abnormalities associated with lesions in specific systems and provide an animal model for studying plasticity in the CNS and for testing innovative therapies.

Aged Monkeys

During the latter part of the second decade of life, macaques develop axonal pathology manifested, in part, as enlarged varicosities and neurite-containing plaques in cortex; older animals exhibit a variety of cognitive/memory deficits, including reductions in short-term memory, difficulties with problem-solving, etc. [Bartus et al., 1978; Davis, 1978,1985]. These animals have plaques that resemble plaques occurring in aged humans and in patients with AD [Wisniewski and Terry, 1973; Wisniewski et al., 1973; Struble et al., 1982,1984b; Price et al., 1985a]. Neurites in plaques are derived from axons and terminals of cholinergic, catecholaminergic, GABAergic, and peptidergic systems [Price et al., 1983; Kitt et al., 1984,1985; Struble et al., 1984b; Walker et al., 1985], but it is not known whether axons/terminals in an individual plaque are derived from one or several sources (for discussion, see Price et al. [Price et al., 1983]). Moreover, it is not clear whether some axons are degenerating and others regenerating, i.e., sprouting, in response to deafferentation by loss of other inputs. In aged macaques, there is a trend for plaque densities to be a better predictor of impaired cognitive function than chronological age [Struble et al., 1985c]. Using available colonies of aged nonhuman primates, it should be possible to characterize the behavior of individual animals and, when these animals die, to correlate abnormalities occurring in brain (e.g., cell loss, altered transmitter markers, evidence of structural pathology involving specific cell types, etc.) with performance on tasks. This approach should provide important new insights into the structural and chemical abnormalities associated with cognitive and memory deficits occurring in aged primates.

Etiological Factors

The cause of AD is unknown, but a variety of factors have been suggested to contribute to the development of AD: age; metabolic abnormalities; familial, genetic, and chromosomal factors; transmissible agents; amyloid deposition; toxins; trauma; and lack of trophic factors.

Age

The incidence of AD increases with age, but the disease is not an invariable consequence of aging. The creative contributions of Sophocles, Verdi, Titian, and Picasso indicate that cognitive processing of the highest order can occur in old age. A more difficult question is: does AD represent an exaggeration of the aging process? [McGeer et al., 1984; Berg, 1985]. In older individuals without overt cognitive impairments, age-associated loss of nerve cells occurs in at least several populations of neurons. In these elderly individuals, scattered neurons show some of the pathologies described above (e.g., NFT, plaques, granulovacuolar degeneration, and Hirano bodies) [Tomlinson et al., 1968], and the distribution of some of these changes is similar to that occurring in elderly individuals without AD [Tomlinson et al., 1968; Hubbard and Anderson, 1981]. Moreover, aspects of these processes occur in aged nonhuman primates, i.e., plaques commonly occur in a variety of monkeys [Wisniewski et al., 1973; Struble et al., 1982,1984a; Kitt et al., 1984; Price et al., 1985a]. Effects of these structural abnormalities of neurons on behavior, cognition, and memory are not well delineated, but recent studies of aged nonhuman primates suggest that a correlation exists between the presence of plaques and the presence of impairment in certain memory tasks [Struble et al., 1985c]. Relationships between these mild age-associated changes and the clinicopathological syndrome of AD deserve further investigation. At present, individuals with AD show much greater frequencies, wider distributions, and greater severities of the structural and chemical pathologies than do aged controls.

Familial, Genetic, and Chromosomal Factors

AD appears to be familial in perhaps 25-40% of cases [Sjogren et al., 1952; Heston et al., 1981; Heyman et al., 1983]; for methodological reviews, see Folstein and Powell [1984]. These individuals tend to have an earlier onset, more rapid progression, more severe structural and chemical pathologies, and an inheritance pattern consistent with an autosomal dominant disease [Heston et al., 1981; Nee et al., 1983]. A recent report has documented the occurrence of AD in genetically identical twins whose mother and maternal grandmother had similar illnesses [Kilpatrick et al., 1983]. In this setting, the disease may have been inherited as a single mutant gene. It has been suggested that the majority of cases of AD may be inherited as an autosomal dominant, which are only fully penetrant at 90 years of age [Folstein and Breitner, 1981]. Difficulties in ascertaining fully informed pedigrees in most cases have confounded the delineation of genetic factors in AD. To date, linkage studies have not shown definite patterns, but, clearly, this is an important area of research. Finally, the risk to individuals is clearly increased when first-degree relatives have the disease [Heston, 1983]. Relatives of persons with AD (particularly AD patients with an onset before the age of 65) have an age-specific risk that is 10-20 times greater than the general population [Heston et al., in press].

As regards chromosomal factors, the frequency of Down's syndrome may be increased among relatives of individuals with AD [Heston et al., 1981; Heyman et al., 1983]. More striking is the observation that some individuals with Down's syndrome show cognitive decline with age [Wisniewski et al., 1978; Lott, 1982] and the brains of older individuals with Down's syndrome frequently exhibit some of the structural and chemical abnormalities typical of AD (i.e., NFT, plaques, cholinergic deficits, and reductions in neurons in the nucleus basalis) [Jervis, 1948; Price et al., 1982; Yates et al., 1983; Wisniewski et al., 1985; Casanova et al., 1985]. It is not known how the presence of an extra chromosome 21 predisposes these individuals to develop an early-onset AD-like illness.

Metabolic Abnormalities

The cortices of individuals with AD show reduced amounts of total protein and decreased protein synthesis (for review, see Sajdel-Sulkowska et al. [1983]), postmortem findings that correlate with images obtained by PET [Bustany et al., 1983]. Recent investigations indicate that total cellular RNA and polyadenylated RNA content are reduced in AD cortex containing plaques and NFT [Sajdel-Sulkowska and Marotta, 1984]. These reductions in RNA appear to be associated with increased activity of alkaline ribonuclease -- a change attributed to an abnormality in the ribonuclease inhibitor complex. Other investigators have suggested that affected cells may show an increase in heterochromatin, which is not as active in transcriptional processes [Crapper et al., 1979]. Other metabolic abnormalities, including those arising from alterations in carbohydrate or calcium metabolism [Perry et al., 1980 P167; Peterson et al., submitted for publication] have been described, but the specificity of these changes remains to be clarified. A variety of alterations have been described in nonneuronal cells outside of the CNS [Blass and Zemkov, in press]. Some of these findings, which could be interpreted to indicate that AD is a metabolic system degeneration, need additional validation, particularly on autopsy-confirmed cases.

Transmissible Agents

To date, AD has not been transmitted to experimental animals [Goudsmit et al., 1980]. Roles of transmissible agents in the pathogenesis of AD are uncertain. Infectious agents could gain access to the brain by a variety of pathways, including local spread, hematogenous routes, retrograde axonal transport, etc. For example, it has been suggested that such agents could reach the brain via the olfactory pathway and spread to the amygdala, hippocampus, and associated cortical regions. AD shares some pathological characteristics (particularly the appearance of amyloid plaques) with the spongiform encephalopathies -- a group of unusual infectious diseases, including scrapie and CJD [Goudsmit et al., 1980; Wisniewski et al., 1981]. (See discussion of CJD.)

Amyloid Deposition

As described above, some patients with AD show amyloid in cerebral vessels [Mandybur, 1975; Glenner et al., 1981; Mountjoy et al., 1982]. From preparations of vessels from brains of individuals with AD and Down's syndrome, a novel β-pleated sheet protein has been identified [Glenner and Wong, 1984], and this protein is strikingly similar to the A4 monomer isolated from plaque amyloid [Masters et al., 1981b]. By analogy with systemic amyloidosis, it has been argued that this unique serum protein, presumed to be manufactured outside the CNS, damages cerebral endothelial cells, enters the brain, and, by mechanisms unknown, leads to the formation of NFT and neurites in plaques [Glenner, 1983a,b]. During the next several years, new approaches derived from protein chemistry and molecular biology should clarify the characteristics, relationships, and vector of evolution of these amyloid deposits.

Toxins

Roles of toxic agents in AD are uncertain. There is some controversy about amounts of aluminum in the brains of patients with AD [Crapper et al., 1973; McDermott et al., 1977,1979; Markesbery et al., 1981]. In some studies, amounts of aluminum have been elevated in the brains of affected patients, and aluminum content does appear to be increased in neurons showing NFT [Perl and Brody, 1980] and, perhaps, in senile plaques [Duckett and Galle, 1976; Perry and Perry, 1985]. However, it is not known whether aluminum accumulates in neurons as a primary process or results because sick cells take up aluminum. Although aluminum may not play a primary role in the pathogenesis of AD, it has been useful in producing experimental models of neurofibrillary pathology which can be studied using a variety of neurobiological approaches [Klatzo et al., 1965; Yates et al., 1976; Crapper et al., 1978; Selkoe et al., 1979; Troncoso et al., 1982,1985,1986; Bizzi et al., 1984].

Trauma

Recent reports suggest that individuals with AD have an increased incidence of histories of head trauma [Heyman et al., 1984; Mortimer et al., 1985]. It is of interest that repeated head trauma, as occurs in boxers, leads to the clinical syndrome of dementia pugilistica, which is associated with the presence of widespread NFT [Corsellis, 1978].

Lack of Trophic Factors

By analogy with studies of nerve growth factor [Levi-Montalcini and Angeletti, 1968; Thonen and Barde, 1980; Barde et al., 1983], it has been suggested that AD may be associated with a lack of a trophic factor normally manufactured by cells in hippocampal or cortical tissues [Appel, 1981; Ojika and Appel, 1983]. In this hypothetical model of AD, abnormalities of target cells in the amygdala, hippocampus, and neocortex are associated with reduced production of a nerve growth factor-like trophic factor; when the factor is not available in sufficient amounts, basal forebrain cholinergic neurons (and possibly other neurons) develop structural abnormalities and then degenerate. It is of interest that, when nerve growth factor is injected into cortex, it is transported retrograde to neurons in the nucleus basalis [Seiler and Schwab, 1984; Mobley et al., 1985] and, in the basal ganglia and basal forebrain, nerve growth factor in brain increases ChAT activity [Mobley et al., 1977; Gnahn et al., 1983]. The roles of trophic factors in AD and related disorders is an exciting new area of investigation.

Treatment Strategies

The demonstration that there are abnormalities in the cholinergic system has led to three major pharmacological strategies designed to restore cholinergic functions. With the L-dopa PD model as a frame of reference, some investigators have tried to increase precursor levels by providing exogenous choline or lecithin. Unfortunately, this therapy has not proved effective. A second approach is to inhibit cholinesterase with physostigmine; this produced a modest improvement of learning and memory in a test circumstance but no sustained improvement in activities of daily living. Another approach is to use muscarinic agonists (e.g., arecholine) that acts directly on receptors on target cells. Again, this approach leads to only minor, brief improvements in test responses. Other studies have evaluated the use of exogenous neuropeptides, metabolic enhancers, and vasodilators. To date, there is no clinically effective pharmacological treatment for the dementia of AD. It is possible that there may be subgroups of patients who would respond to some of the above therapies. If these subgroups could be accurately delineated, therapeutic responses might be more satisfactory. It should be emphasized that animal models with lesions of transmitter-specific circuits may be useful for testing therapeutic approaches directed toward restoration of functions of damaged transmitter systems.

PARKINSON'S DISEASE

PD, classical paralysis agitans [Parkinson, 1817], is one of the most common degenerative neurological diseases occurring in the elderly. Approximately 400,000 individuals are affected in the United States [Elridge and Ince, 1984]; the incidence of PD is 20 per 100,000 population, and this incidence has not changed since 1967 [Rajput et al., 1984].

Clinical Manifestations

This disorder, which usually appears in the sixth decade, is characterized by slowness of voluntary movements (bradykinesia), rigidity, and tremor [Marsden, 1982; Penney and Young, 1983]. Available evidence suggests that PD is a heterogeneous disorder [Lieberman et al., 1979; Zetusky et al., 1985], and at least two subgroups have been identified: one group of patients has an earlier onset of disease, slower progression, and tremor with relatively preserved intellectual functions; a second group shows bradykinesia and cognitive impairments, and these individuals tend to have later-onset disease, dysarthria, dysphasia, a more rapid course, and a resistance to L-dopa. At least 30% of PD patients develop dementia [Lieberman et al., 1979; Mayeux and Stern, 1983], and manifestations include impairments in memory, constructional abilities, attention, digit span, and abstractions [Boller et al., 1980; Mayeux, 1982]. Some correlations exist between the presence of cognitive abnormalities (particularly visuospatial skills and psychomotor speed) and the the severity of motor signs (particularly bradykinesia, postural instability, and gait disability) [Mayeux et al., 1981; Mortimer et al., 1982; Zetusky et al., 1985].

Laboratory Studies

In some patients with PD, cortical atrophy has been demonstrated by pneumoencephalography [Svennilsen et al., 1960; Selby, 1968; Gath et al., 1975] and computerized tomography [Schneider et al., 1977]. In individuals with hemiparkinsonism, [^{15}O] PET scans showed no change in global hemispheric blood flow but demonstrated reductions in blood flow in mesocortical regions as well as asymmetries in pallidal blood flow [Perlmutter and Raichle, 1985]. In demented PD patients, [^{18}F] fluorodeoxyglucose PET scans have demonstrated correlations between the severity of dementia and brain hypometabolism [Kuhl et al., 1984].

Brain Abnormalities

Some patients with PD have evidence of cerebral atrophy [Alvord, 1971], but the principal abnormalities are detectable by histopathological and neurochemical analyses.

Dopaminergic Neurons of the Substantia Nigra, Pars Compacta

The classical pathology of PD occurs in the SNpc, which is grossly pale and contains reduced numbers of nerve cells [Forno, 1982; Marsden, 1982]. Some surviving nigral neurons contain Lewy bodies -- concentric, intracytoplasmic inclusions that immunocytochemical preparations have demonstrated to contain neurofilament antigens [Goldman, 1983]. In classical PD, nerve cells in the SNpc rarely contain NFT; this pathology is more commonly observed in postencephalitic parkinsonism [Forno, 1982]. Abnormalites of SNpc are associated with reductions (80-95%) in dopaminergic markers in the striatum

[Riederer and Wuketich, 1976; Hornykiewicz, 1982]. The ratio of striatal dopamine to its metabolite homovanillic acid (an index of dopamine turnover and release) is decreased, a finding interpreted to suggest that surviving neurons in the SNpc increase their activity in compensation for loss of nerve cells. In addition, striatal neurons respond to dopaminergic deafferentation by increasing the number of dopamine receptors [Marsden, 1982].

Other Catecholaminergic Systems

Some PD patients have pathology in nonnigral catecholaminergic pathways. The number of dopaminergic neurons in the ventral tegmental area is reduced [Javoy-Agid et al., 1984; Uhl et al., 1985] with 50-60% reductions in dopaminergic markers in mesolimbic and mesocortical target fields [Javoy-Agid and Agid, 1980; Hornykiewicz, 1982; Scatton et al., 1983]. Similarly, the number of neurons in the locus coeruleus may be diminished [Forno, 1982] with reduced (50%) noradrenergic markers in cortex [Scatton et al., 1983; Agid and Javoy-Agid, 1985]. Finally, serotonergic markers, reflecting innervation from neurons located in the raphe complex, may also be reduced in subcortical and cortical regions [Scatton et al., 1983].

Other Neuronal Systems

Other transmitter systems (besides catecholaminergic neurons) may be affected in PD. In the basal ganglia, changes have been documented in markers of several cell populations, including cells using as neurotransmitters: GABA; met-enkephalin; leu-enkephalin; substance P; and bombesin [Agid and Javoy-Agid, 1985 Bissette et al., 1985a]. Neurotensin receptors, which are believed to be located on SNpc neurons [Palacios and Kuhar, 1981], are reduced in the SNpc of PD patients [Uhl et al., 1984]. Relationships of these alterations in peptidergic markers to clinical signs, particularly dementia, are unknown.

Some demented patients with PD show reductions in nerve cells in the basal forebrain cholinergic system [Arendt et al., 1983; Candy et al., 1983; Whitehouse et al., 1983] and a decrease in cortical cholinergic markers [Ruberg et al., 1982]. Somatostatin-like immunoreactivity may be decreased in hippocampus and neocortex [Epelbaum et al., 1983], and preliminary studies from our laboratory suggest that cortical CRF levels may be reduced in some patients with PD. In this disease, abnormalities of the basal forebrain cholinergic system [Boller et al., 1980; Arendt et al., 1983; Whitehouse et al., 1983; Candy et al., 1983] can be, but are not necessarily, associated with typical features of AD (e.g., senile plaques and NFT in amygdala, hippocampus, and neocortex) [Alvord et al., 1974; Hakim and Mathieson, 1979; Boller et al., 1980; Boller, in press; Quinn et al., in press]. The presence of superimposed AD-type pathology certainly does not account for all cases of dementia in PD [Perry et al., 1983; Ball, 1984; Nakano and Hirano, 1984; Quinn et al., in press]. Finally, some demented individuals with PD show many Lewy bodies in various forebrain regions, including neocortex. These various lines of evidence indicate that several different types of dementia occur in the setting of PD.

Clinicopathological Correlation

The bradykinesia and rigidity of PD have been attributed to lesions in the SNpc, but the exact ways in which these abnormalities interfere with motor programs are not known. The presence of bradykinesia correlates best with reduced dopamine and homovanillic acid in the caudate, while the presence of tremor is thought to parallel reductions in homovanillic acid in pallidum [Bernheimer et al., 1973]. The slowing of thought processes (bradyphrenia) may be related to lesions in nonnigral monoaminergic cell groups, particularly neurons of the ventral tegmental area of the dopaminergic mesocortical and mesolimbic systems [Javoy-Agid and Agid, 1980]. In addition, aspects of the dementia syndrome of PD may result from abnormalities of several neuronal populations: nerve cells in the basal forebrain cholinergic system; neurons of other brainstem monoamine systems, including cells in the locus coeruleus and raphe complex; cortical somatostatin and somatostatinergic and CRF-containing neurons; and, possibly, other neuronal systems intrinsic to hippocampus and neocortex.

Animal Models

Toxic Injury of the Nigrostriatal Dopaminergic System

In humans and monkeys, systemic administration of MPTP produces akinesia, rigidity, flexed posture, and postural tremor; these abnormalities can be reversed by treatment with L-dopa [Davis et al., 1979; Burns et al., 1983; Langston et al., 1984a; Ballard et al., 1985; Langston, 1985; Snyder and D'Amato, 1986]. Although not overtly demented, human patients with MPTP-induced parkinsonism show cognitive deficits, including alterations in general intellectual functions, constructions, category naming, and frontal lobe functions [Stern and Langston, 1985].

Clinicopathological studies indicate that this toxin preferentially damages the nigrostriatal dopaminergic system [Burns et al., 1983; Langston et al., 1984a; Kitt et al., in press]. After gaining access to brain, MPTP binds to monoamine oxidase B, an enzyme enriched in certain regions in the CNS (including the striatum) [Parsons and Rainbow, 1984], and is converted to 1-methyl-4-phenylpyridinium (MPP+), the toxic metabolite [Langston et al., 1984b] that is taken up by high-affinity dopamine uptake systems located on terminals of SNpc nerve cells [Javitch et al., 1985]. Inhibitors of MAOB activity and dopamine uptake can block the neurotoxic effects of MPTP [Langston et al., 1984a; Javitch et al., 1985]. At high-dose levels, MPTP selectively destroys SNpc neurons with secondary reductions in dopaminergic markers in the striatum. At lower dose levels, some nigral neurons degenerate, but other SNpc neurons suffer damage to distal axons [Kitt et al., in press]. This chemical axotomy, perhaps mediated by a 6-hydroxydopamine-like effect, appears to lead, by a retrograde signaling mechanism, to reduced activity of tyrosine hydroxylase in perikarya [Kitt et al., 1985]. Some injured neurons eventually die, but some recover, and their axons/terminals possibly reinnervate the striatum. This process may account for some of the restoration of motor function occurring in certain animals.

The MPTP model provides a useful system to examine, using in vivo imaging techniques, the evolution of changes in pre- and postsynaptic markers in basal ganglia, to study the physiology of dopamine-denervated basal ganglia circuits, to delineate mechanisms of toxic injury of neurons, to examine regenerative processes in the CNS, and to develop and test new therapeutic approaches, including neural grafts [Dunnett et al., 1983; Redmond et al., 1985].

Etiological Factors

The etiology of PD is unknown (for review, see Calne et al. [1984] and Calne and Langston [1983]). A variety of factors, including environmental agents (viruses and toxins), aging, genetic contributions, and metabolic abnormalities, have been suggested to play roles in PD.

Environmental Agents

The observation that many patients with von Economo's encephalitis lethargica, which occurred from 1919 through 1930 [Duvoisin and Yahr, 1965], developed a parkinsonian syndrome, led to the hypothesis that PD was due to a viral infection [Poskanzer and Schwab, 1963]. Although the number of cases of postencephalitic parkinsonism declined significantly during the past several decades, the incidence of classical PD has not changed [Rajput et al., 1984; Eldridge et al., in press], suggesting that PD is not a delayed expression of encephalitis lethargica. Moreover, histological findings in PD are not characteristic of infection and, to date, injection of affected brain tissue into animals has not transmitted a disease resembling PD [Duvoisin, 1982].

Stimulated by investigations of intoxication with MPTP, it has been suggested that environmental toxins may be implicated in some cases of PD [Calne and Langston, 1983]. If neurotoxic substances exist in the environment, exposure to these agents could lead to selective and irreversible injury of the nigrostriatal system. Exposure could occur in middle life, and clinical signs could only be expressed after significant age-associated reductions in the number of dopaminergic neurons and striatal dopamine levels fell below threshhold. To date, there is no direct evidence for such toxins causing classical PD, but this issue deserves further investigation.

Aging

There appear to be age-related reductions in the number of nigal neurons and in dopamine content in striatum [Carlsson and Winblad, 1976; McGeer et al., 1977]. It has been suggested that, if this process were accelerated by disease, a deficiency of striatal dopamine would exceed threshhold and the patient would develop symptoms of PD [McGeer et al., 1977].

Genetic Contributions

There does not appear to be a strong genetic basic for the majority of cases of PD: the concordance rate for twins is low; and few well-characterized cases can be considered familial.

Metabolic Abnormalities

It has been suggested that the formation of free radicals, possibly related to catecholamine synthesis, may play a role in the damage of nigral neurons [Barbeau et al., 1984].

Treatment Strategies

In general, motor signs in PD patients respond to L-dopa alone or to a combination of L-dopa and decarboxylase inhibitors. These therapies have not changed overall mortality rates [Rajput et al., 1984]. Subsequently, this strategy has not proved to be effective in the treatment of the dementia of PD, although some investigators have reported that L-dopa has produced transient improvements in mental status on neuropsychological test performance [Meier and Martin, 1970; Drachman and Stahl, 1975; Mayeux, 1982]. Thus, it does not appear that L-dopa produces any long-term difference in the mental status of PD patients [Markham et al., 1974; Mayeux, 1982]. In severely demented individuals, L-dopa can have undesirable side effects, including agitation, hyperkinesia, and hallucinations [Mayeux, 1982]. Available evidence derived from treatment strategies suggests that the dementia occurring in PD is a complex disorder which does not respond to therapies that improve bradykinesia and ridigity.

HUNTINGTON'S DISEASE

This inherited neurological disease is characterized by involuntary movements (chorea) and dementia. The prevalence of HD is approximately ten per 100,000, and the majority of the population at risk is caucasian. Approximately 20,000 persons in the United States have clinical disease, and 100,000 other individuals are at risk. Because the clinical features of HD are usually not expressed until middle life, a significant number of potentially at-risk individuals have already had children and, perhaps, have passed along the gene before they know whether they carry the HD gene. Recent exciting studies in the molecular biology of HD [Gusella et al., 1983,1984] suggest that a test may soon be available for the HD gene [Wexler et al., 1985].

Clinical Manifestations

Abnormal movements and behavioral changes are usually the initial manifestations of the illness, and, over years, the patient develops the classical syndrome of HD [Martin, 1984]. The disease usually begins in the fourth decade, with variations occurring between kindreds. Mental abnormalities consist of cognitive impairments, memory loss, personality changes, and a variety of psychological symptoms including irritability and depression [Bruyn, 1968; Folstein and Folstein, 1983; Folstein et al., 1985]. Care of these patients and their families is a challenge to physicians [Marsden and Fahn, 1982; Shoulson, 1982]. Some patients commit suicide. Death usually occurs 15 years after the onset of illness.

Laboratory Studies

Computerized tomography commonly shows reductions in the volume of the striatum, particularly the caudate nucleus, and PET has demonstrated decreased metabolic activity in striatum [Kuhl et al., 1982], a change that apparently precedes alterations in striatal volume.

Recombinant DNA techniques to delineate genetic linkage markers have demonstrated a close linkage between the HD locus and a DNA fragment, G8, located on the short arm of chromosome 4 [Gusella et al., 1983,1985]. In these studies, DNA was digested with restriction endonucleases was separated by electrophoresis (Southern blots); subsequently, radioactive probes were used to examine samples of DNA fragments from different individuals, and hybridization polymorphisms were assessed and analyzed for their linkage to the HD gene [Gusella et al., 1985]. These investigations have demonstrated that the G8 marker is a 17.6 kd unique-sequence fragment of anonymous DNA localized to chromosome 4 within 5-10 centimorgans of the HD gene. The odds in favor of linkage to HD are more than one quadrillion to one in two large pedigrees that have been analyzed in the United States and in Venezuela [Wexler et al., 1985]. The G8 marker is not sufficiently close to the gene so that one hapelotype invariably segregates with the presence of HD. These studies have raised the question as to whether HD may be heterogeneous at a genetic level. To examine the hypothesis that some of the phenotypic variability in HD between families is due to mutation at different loci, linkage analyses were undertaken in two large HD kindreds that differed in ethnic origin, age of onset, and neurological and psychiatric features [Folstein et al., 1983]. Both families showed linkage of the HD locus to the G8 probe, several recombinants were documented in each family, and the best estimate of recombination fractions for the two families was 6% with a 95% confidence interval of 0-12%. Use of the G8 probe for presymptomatic testing in these kindreds would have resulted in a 12% error rate in the genotype assignment at the HD locus. Nevertheless, during the next few years, the discovery of this linkage marker should lead to the development of a laboratory test that can be used to detect the presence of the HD gene in prenatal and presymptomatic individuals.

Brain Abnormalities

Basal Ganglia

In HD, the striatum is atrophic [Lange et al., 1976; Lange, 1981]. Several types of abnormalities have been detected in striatal neurons. Golgi studies suggest that some dendrites of medium-sized spiney neurons are abnormal and that changes occur in sizes, shapes, and densities of spines of these cells [Graveland et al., 1985]. There is a loss of medium-sized spiney I and II neurons (GABAergic, enkephalinergic, and substance P nerve cells) and larger intrinsic spiney II cholinergic neurons [Gale et al., 1978; Emson et al., 1980; Martin, 1984]. Aspiney I (somatostatinergic) nerve cells appear to be relatively spared [Aronin et al., 1983].

Loss of striatal efferents to basal ganglia targets is associated with reductions in GABA, met-enkephalin, and substance P markers in substantia nigra and globus pallidus [Gale et al., 1978; Emson et al., 1980]. GABA, benzodiazepine, dopaminergic, and muscarinic cholinergic receptors, as well as [^{3}H] glutamate binding, are reduced in striatum [Bird, 1980; Greenamyre et al., 1985], but the density of dopaminergic terminals and concentrations of dopamine are increased [Bird, 1980]. In the GABA-denervated globus pallidus and nigra, GABA and benzodiazepine receptors are increased, presumably due to denervation supersensitivity [Whitehouse et al., 1985].

Cerebral Cortex

The thickness of the cerebral cortex, particularly in the frontal regions, is often reduced [Lange, 1981]. In frontal and parietal lobes, the number of neurons is reduced in layers III, V, and VI. Some of these neurons may be part of the cortical-striatal system (see below). The number of benzodiazepine receptors is increased in frontal cortex, but, otherwise, neurochemical studies have not identified major changes in transmitter markers associated with these lesions. Some of these cortical neurons may use excitatory amino acids or as yet unknown peptides as transmitters, and such abnormalities would not be readily detected with currently available techniques.

Other Neuronal Systems

In contrast to lesions in basal ganglia and cortex, many other cell groups (including neurons of the basal forebrain cholinergic system [Clark et al., 1983]) are relatively spared.

Clinicopathological Correlations

Chorea apparently results from altered synaptic circuits within basal ganglia, particularly loss of neurons intrinsic to striatum or cells projecting to substantia nigra and pallidum [Marsden and Fahn, 1982; Penney and Young, 1983]. Cognitive deficits occurring in patients with HD have been suggested to reflect, in part, degenerative changes in nerve cells in the caudate nucleus, a hypothesis which receives support from the observation that the presence of dementia in HD correlates with evidence of hypometabolism in the caudate nucleus [Kuhl et al., 1982]. Lesions of cortical neurons and/or cortical-striatal circuits, which link dorsolateral, prefrontal, and lateral orbitofrontal cortices with caudate [Alexander et al., in press]), may also contribute to cognitive abnormalities [Divac, 1984].

Animal Models

Unfortunately, an inherited animal disorder resembling HD has not yet been identified. However, investigators have induced hyperkinesias by a variety of experimental brain lesions, and certain features of HD can be produced by direct injection of kainic acid, an excitotoxin, into striatum [Coyle and Schwartz, 1976]. This procedure destroys neurons whose perikarya are located in striatum but spares fibers of passage. Neurochemical deficits are similar to those identified in HD (i.e., reductions occur in markers for intrinsic cholinergic neurons, for striatonigral GABAergic and substance P pathways, and for striato-pallidal enkephalinergic systems, but fibers of the nigrostriatal dopaminergic system are spared). Although these animals do not develop chorea, locomotion is impaired, and some animals show deficits in performance on tests of learning and memory [Sanberg and Coyle, 1984].

Etiology

HD is an autosomal dominant disorder, and each child of an affected parent has a 50% risk of inheriting the HD gene, which is thought to have a 100% penetrance. As described above, recent molecular genetic investigations have identified a restriction fragment-length polymorphism that has been mapped to chromosome 4 and linked to the HD gene [Gusella et al., 1983,1985]. Localization of this polymorphism linked to the HD gene represents the first example in which recombinant DNA technology has been used to delineate a gene without knowledge of the gene product. This discovery was made possible, in substantial part, because of the availability of large family pedigrees in which members of single families shared a common genetic anomoly. This discovery is an excellent example of the results of close cooperation between clinicians and basic scientists. In the future, it should be possible, using cloning strategies based on localization of the HD gene to chromosome 4, to isolate and identify the defective gene [Gusella et al., 1985]. Once the gene is cloned, it can be characterized, and the abnormal gene product can be identified. Other techniques, including immunocytochemistry or in situ hybridization, can then be used to localize the protein or its mRNA to specific regions and cells in brain. Perhaps, at this stage, we will be able to understand how the etiological factor occurring in HD, a defective gene, leads to structural and functional abnormalities in specific regions of brain and how these cellular pathologies cause chorea and dementia in patients with HD.

Treatment Strategies

At present, there is no cure for HD, and drugs do not slow the progression of this illness [Shoulson, 1979,1982].

CREUTZFELDT-JAKOB DISEASE

CJD, a transmissible form of dementia associated with myoclonus and motor dysfunction [Roos et al., 1973], is caused by an unusual agent, frequently referred to as an "unconventional virus" or a "prion" [Gajdusek, 1984,1985b; Prusiner, 1984,1985]. The disease has an annual incidence of approximately one per million of population, occurs worldwide, and does not show a seasonal incidence [Masters et al., 1979a; Johnson, 1982; Gajdusek, 1984]. In some cases (perhaps 10%), susceptibility for the disease appears to be inherited as an autosomal dominant trait [Masters et al., 1979b]; in addition, CJD shows some features in common with the Gerstmann-Sträussler syndrome, a rare familial disorder manifest as a chronically progressive ataxia and dementia [Masters et al., 1981a]. Histopathological studies have demonstrated that CJD is one of the spongiform encephalopathies (a term derived from the presence of characteristic vacuolation of neuronal processes) [Beck et al., 1969; Beck and Daniel, 1979], a group of chronic, progressive, and invariably fatal diseases of the CNS. Other disorders of this type, which are also caused by similar transmissible agents, include kuru (occurring in Fore tribesmen of New Guinea) and two animal disorders (scrapie and mink encephalopathy) [Gajdusek, 1985].

Clinical Manifestations

Patients with CJD develop a rapidly progressive dementia associated with ataxia and myoclonic jerks [Roos et al., 1973; Adams and Victor, 1985; Gajdusek, 1985]. The majority of affected individuals is beyond middle age, but the disease can occur in younger individuals. Early manifestations are characterized by changes in intellectual, emotional, and behavioral functions, usually associated with some degree of incoordination. Eventually, patients become profoundly demented and exhibit myoclonus and extreme sensitivity to a variety of stimuli. CJD progresses rapidly, and the majority of patients dies within a year of onset.

Laboratory Studies

In the majority of patients, the EEG pattern is distinctive, changing over the course of the disease from a diffuse, nonspecific slowing to one of high-voltage, synchronous, sharp waves followed by burst suppressions on an increasingly flat background [Adams and Victor, 198]. The CSF does not show a pleocytosis or elevation of protein, but some patients have antibodies directed against neurofilament proteins in CSF [Sotelo et al., 1980; Gajdusek, 1985]. Significantly, this infection does not evoke responses of the immune system (i.e., there is no peripheral leukocytosis, antibody response, CSF pleocytosis, increase in CSF protein, or inflammation of brain parenchyma).

Brain Abnormalities

CJD affects the grey matter in a variety of brain regions, including the cerebrum and cerebellum [Beck et al., 1969; Beck and Daniel, 1979; Malamud, 1979]. Spongiform vacuolation (*status spongiosus*) involves dendrites, axons, and cell bodies of neurons and, to a lesser extent, glial cells. Neuronal loss and astrogliosis-astrocytosis are usually very conspicuous. Some patients develop amyloid plaques. In classical cases, there is no evidence of inflammatory response in brain tissue. Virus particles have not been identified, but recent studies have demonstrated 10-20 nm fibrils, termed "scrapie associated fibrils" in brains of CJD patients and in brains of animals with experimental CJD [Merz et al., 1981,1983a-c,1984]. These fibrils are readily distinguishable from PHF that occur in AD but do show histochemical reactions typical of amyloid [Prusiner et al., 1983]. Purified fractions from brains of individuals with CJD yield a protein, PrP (see below), which appears to be a component of the rods or fibrils occurring in the brain [Bockman et al., 1985]. Because CJD is a transmissible disorder, precautions should be taken in the care and handling of materials from patients with CJD [Baringer et al., 1980].

Clinicopathological Correlations

The clinical symptoms and signs of CJD are attributed to diffuse and widespread pathology, involving the cerebrum, diencephalon, brainstem, and cerebellum.

Etiology

Agents causing the spongiform encephalopathies have unique physical, chemical, and biological properties (i.e., they are filterable and resist inactivation by conventional techniques, e.g., treatment with disinfectants, aldehydes, antiviral agents, nucleases, ultraviolet radiation, and ionizing radiation). In infected hosts, these agents replicate at low rates, and long periods elapse before they reach titers associated with cell injury.

Aspects of CJD resembles kuru, a disease occurring in members of the Fore tribe in New Guinea. Affected individuals develop progressive cerebellar ataxia and weakness, and die within 3-6 months [Gajdusek and Zigas, 1959]. Brain lesions are remarkably similar to those occurring in CJD and in scrapie. Similarities between scrapie and kuru led Hadlow [Hadlow, 1959] to suggest that kuru might be a transmissible disease. Innoculation of brain tissue from kuru patients into chimpanzees caused disease in recipients after a latency of 18-36 months [Gajdusek et al., 1977]; more recently, the disease has been experimentally transmitted between chimpanzees and to New and Old World monkeys, guinea pigs, and laboratory mice [Gajdusek, 1985a]. Subsequent studies, using similar protocols, demonstrated that specimens of brain from individuals with CJD or the Gerstmann-Straüssler syndrome could also be used to transmit disease to laboratory animals [Masters et al., 1981a; Gadjusek, 1985a]. Clinical signs and pathological lesions of sheep or goats infected with CJD are indistinguishable from those of scrapie.

Several types of direct transmission of CJD have been reported in humans. CJD has occurred in the recipient of a corneal graft from a donor with CJD and in individuals who received CJD-contaminated depth electrodes implanted in brain [Duffy et al., 1974; Bernoulli et al., 1977]. Recently, a CJD-like disease has occurred in several young patients who received human growth hormone for treatment of the complications of dwarfism [Brown et al., 1985; Gibbs et al., 1985; Koch et al., 1985; Norman, 1985]. The source of this infection is believed to be growth hormone extracted from human pituitary glands which presumably were infected with the CJD agent. It has been suggested that purification techniques between 1966 and 1976 may not have been adequate to inactivate the agent, and the program to produce and distribute the hormone has been suspended.

The etiology and pathogenesis of spongiform encephalopathies are reviewed in detail in the section (below) dealing with scrapie.

Scrapie: An Animal Model of Spongiform Encephalopathy

Clinical Manifestations

Scrapie, occurring in sheep and goats, is the prototype for slow infections caused by unconventional viruses [Hadlow et al., 1979; Johnson, 1982]. Animals develop ataxia, wasting, and pruritis and tend to scrape their fleece, presumably due to unusual cutaneous sensations. Animals also exhibit behavioral changes (hyperexcitability or somnolence), grinding of teeth, and rapid movements of lips and tongue. Usually afebrile, sheep become progressively debilitated and ataxic; death ensues in weeks to months.

Laboratory Studies

The CSF does not show a pleocytosis; no abnormalities have been detected in peripheral blood.

Neuropathology

Pathology in the CNS is similar to that occurring in CJD [Hadlow, 1959; Beck et al., 1969; Baringer and Prusiner, 1978; Beck and Daniel, 1979; Baringer et al., 1979]. Many neurons are vacuolated, and there is astrocytosis–astrogliosis, most conspicuous in the grey matter of the cerebellar cortex, pontine nuclei, midbrain, and diencephalon. Localized amyloid deposits and senile plaques can be induced by intracerebral inoculation of preparations of the scrapie agent [Wisniewski et al., 1981].

Pathogenesis

Genetic factors and the strain of scrapie agent appear to play an important role in determining susceptability, the length of the incubation period, and the character and distribution of lesions [Dickinson and Fraser, 1979]. It is not known how the natural disease is transmitted, but intimate contact between young lambs and infected adults appears to be an important factor. Experimental studies suggest that natural infection occurs via an oral route. Goats reared in contact with infected sheep may develop scrapie, and mink-fed tissue from infected sheep develop a spongiform encephalopathy (mink encephalopathy).

During the past few years, considerable progress has been made in studies of the unusual agents associated with the pathogenesis of spongiform encephalopathies [Prusiner, 1984; Gajdusek, 1985; Prusiner et al., 1985]. Electron microscopic studies disclosed scrapie-associated fibrils or prion filaments (typically 10-20 nm in diameter and 100-200 nm long) in brain tissue infected with scrapie, and similar fibrils have been identified in CJD [Merz et al., 1981,1983a-c,1984; Prusiner et al., 1983]. There appear to be some biochemical differences between scrapie-associated fibrils [Bendheim et al., 1984; Kascsak et al., 1985]. These fibrils are enriched in a 27-30 kd protein, termed PrP27-30. This sialoglycoprotein [Bolton et al., 1982,1985; Prusiner et al., 1984] is derived, by limited proteolysis (with proteinase K) from PrP33-35, a protein present in scrapie-infected brain. Under the same conditions of proteolysis, the cellular protein 33-35C, which is presented in unaffected controls, is completely degraded [Meyer et al., in press]. PrP is present in fibrils and can be labeled with antibodies; moreover, these fibrils aggregate to form amyloid-like birefringent rods [Prusiner et al., 1983; DeArmond et al., 1985]. Recent evidence indicates that PrP is encoded by a host gene and is expressed in normal and in infected animals [Oesch et al., 1985]. A clone encoding PrP 27-30 was obtained from a cDNA library of scrapie-infected hamster brain. Southern blots with these probes show a single gene with restriction patterns identical in normal and infected animals, and PrP mRNAs can be detected in control and infected hamsters. In purified preparations of fibrils, PrP-related nucleic acids were not demonstrated -- an observation interpreted to indicate that PrP 27-30 is not encoded by a nucleic acid carried within the infectious particle [Oesch et al., 1985]. It has been suggested that scrapie infection may be associated with the accumulation of PrP35SC and that this protein may be important in the pathogenesis of the neurological disease [Meyer et al., in press]. PrP is apparently synthesized in neurons [Kretzschmar et al., 1986], but relatively little direct information is available about the relationships of this protein to the transmissibility of disease or about *in vivo* processing of PrP that leads to the formation of amyloid-like filaments. It should be noted that prion proteins are present in brains from humans with CJD [Bockman et al., 1985; Prusiner et al., 1985], and the prion protein in CJD shares physical properties and antigenic determinants with the scrapie protein [Bendheim et al., 1985].

Treatment Strategies

The disease is invariably fatal, and no specific treatments are available [Gajdusek, 1985]. Therapeutic trials with antiviral agents have not been effective. This infectious process is not altered by treatment with cortisone, radiation, cytotoxic drugs, or antileukocyte serum [Gajdusek, 1984a,1985b]. Because CJD is a transmissible disorder, precautions should be taken in the care and handling of materials from patients with CJD [Baringer et al., 1980].

ACQUIRED IMMUNE DEFICIENCY SYNDROME

AIDS, a disorder first reported in the United States in 1981 (see Curran et al. [1985]), is due to infection with a retrovirus, termed ARV, LAV, or HTLV-III [Barre-Sinoussi et al., 1983; Gallo et al., 1984]. The disease is characterized by lymphopenia, low levels of T-helper/inducer lymphocytes (T4), and generalized lymphadenopathy [Lane et al., 1985]. This infection, which occurs in certain high-risk groups, including users of intravenous drugs, homosexuals, and hemophiliacs following transfusions [Curran et al., 1985], is associated with a variety of neurological syndromes, with dementia being particularly conspicuous [Nielson et al., 1984; Epstein et al., 1985a,b; Shaw et al., 1985; Johnson and McArthur, in press; Navia et al., in press a,b; Price et al., in press b]. The progressive impairment in cognitive processes, memory, etc., which may be due to neurotropic retrovirus infection of the brain [Shaw et al., 1985], has been termed "the AIDS-dementia complex" [Navia et al., in press b].

Clinical Neurological Manifestations

When a patient is first evaluated by a physician, neurological complaints are noted in approximately 30-40% of AIDS patients. Impaired concentration, psychomotor slowing, and memory loss are early symptoms that are frequently associated with malaise, lethargy, loss of sexual drive, behavioral changes, and withdrawal from personal and professional contacts [Snider et al., 1983; Jordan et al., 1985; Navia et al., in press b]. Eventually, the majority of these patients develop dementia, mutism, incontinence, and motor abnormalities. Approximately 60-70% of these patients have a generalized encephalopathy that appears to be not directly related to superimposed opportunistic infections or neoplasms involving brain [Snider et al., 1983; Moskowitz et al., 1984; Levy et al., 1985] but appears to be the result of a direct retrovirus infection [Epstein et al., 1985b; Ho et al., 1985; Levy et al., 1985; Shaw et al., 1985; Navia et al., in press a,b; Price et al., in press b]. A similar process occurs in children with AIDS who develop neurological signs, including loss of motor milestones and abnormalities in intellectual abililties [Shaw et al., 1985; Epstein et al., 1985a].

Laboratory Studies

In demented AIDS patients, the EEG may be abnormal, with the most common pattern being a diffuse, nonspecific slowing of electrical activity [Levy et al., 1985]. Computerized tomography and magnetic resonance imaging frequently demonstrate cortical atrophy [Snider et al., 1983; Epstein et al., 1985b; Levy et al., 1985], and magnetic resonance imaging sometimes detects focal abnormalities in white matter [Navia et al., in press a] that may not appear on computerized tomographic scans. Conventional studies of CSF have not disclosed specific abnormalities: CSF proteins are mildly increased (50-100 mg dl); some patients show oligoclonal bands in CSF; mild reductions have been noted in glucose levels; and mononuclear cells may be increased in number. Antibody titers are consistent with infection with retrovirus infection, and virus can be isolated from CSF [Ho et al., 1985; Levy et al., 1985], as well as from blood, semen, saliva, and tears.

Brain Abnormalities

Autopsies of AIDS patients have demonstrated pathological changes in the CNS in >75% of cases [Nielsen et al., 1984]. The most frequent abnormality in brain is an encephalitis that occurs in approximately 50% of patients with clinical manifestations of progressive dementia [Navia et al., in press b]. Brains of demented patients show meningeal fibrosis, mild-to-moderate dilatation of ventricles, and reductions in the volume (atrophy) of cerebral white matter and cortical gyri. Histopathological abnormalities occur predominantly in the white matter and subcortical structures [Navia et al., in press b]. Microglial nodules are present in grey and white matter, and some of these nodules are associated with cells (? astrocytes) showing inclusions. Myelin stains show diffuse pallor, and, with more severe disease, vacuolation of white matter. Perivascular foci of demyelination are present, particularly in frontal and temporal regions. Axonal pathology has been identified in some cases. Brain lesions may be associated with reactive astrocytes, lipid-containing macrophages, and multinucleated cells (? macrophages) [Snider et al., 1983]. Although some of these multinucleated cells have been attributed to infection with cytomegalovirus, many of these multinucleated cells resemble syncitial cells induced by retrovirus infection in culture [Popovic et al., 1984; Shaw et al., 1985]. Ultrastructural studies suggest that macrophages, multinucleated giant cells, and astrocytes may contain unusual, coated particles (90-140 nm) closely resembling viral particles identified in culture [Epstein et al., 1985a].

In the brains of some individuals with the AIDS-dementia complex, Southern-blot hybridization demonstrated the presence of integrated and nonintegrated proviral DNA in brain tissue [Ho et al., 1985; Levy et al., 1985; Shaw et al., 1985]. Viral nucleic acid sequences are enhanced in brain compared to other tissues [Shaw et al., 1985]. *In situ* hybridization has shown the presence of viral RNA in cells [Shaw et al., 1985], but the character of the cells affected by virus has not been clarified. Moreover, it is not known whether infected mononuclear cells/macrophages carry the virus into the brain or whether cell-free virus enters brain and directly infects neural cells. Future studies will be needed to determine the cell type or types infected with retrovirus, the cellular location of virus, the mechanisms of viral tropism for neural cells, the structural and chemical changes occurring in infected cells, and the relationships of these processes to clinical signs and symptoms.

In addition to the viral infection described above, patients with AIDS frequently develop a variety of chronic opportunistic infections of the CNS, including toxoplasmosis, cryptococcosis, candidiasis, tuberculosis, aspergillosis, etc. Some patients have disseminated infection with cytomegalovirus, and, in some of these cases, immunohistochemical stains have detected cytomegalovirus antigen in the cytoplasm of large inclusion-bearing cells [Nielsen et al., 1984]. However, the cytomegalovirus-type pathology does not appear to be the principal cause of the AIDS-dementia complex [Navia et al., in press b].

Clinicopathological Correlations

To date, clinicopathological correlative studies suggest that the dementia occurring in individuals with AIDS is due to widespread involvement of cerebrum.

Etiology

AIDS is caused by infection with a retroviruses referred to as HTLV-III, LAV, and AIDS-associated retrovirus [Barre-Sinnoussi et al., 1983; Gallo et al., 1984; Popovic et al., 1984; Levy et al., 1985]. The retrovirus family consists of viruses that contain an RNA-dependent DNA polymprase (reverse transcriptase). Molecular hybridization and heteroduplex analysis suggest that the nucleotide sequence of AIDS-associated retrovirus shows greater homology with visna virus, a member of the subfamily *Lentiviridae* than do HTLV-I and HTLV-II. Moreover, the ultrastructure of HTLV-III resembles more closely the structure of visna than the other HTLVs.

Animal Models

The virus causing AIDS is closely related to visna virus, a member of the family of nononcogenic lentiviruses [Gonda et al., 1985; Narayan and Cork, 1985] that are associated with persistent viral infection and produce multisystem disease. The best known of this group is a laboratory-adapted strain, visna virus, which experimentally produces chronic neurological disease in sheep. The natural infection is associated with varying degrees of encephalitis (visna), pneumonia (Maedi), and arthritis [Sigurdsson and Palsson, 1958; Sheffield et al., 1980]. A related virus in goats, caprine arthritis encephalitis virus, produces chronic degenerative neurological disease, pneumonia, and arthritis. These viruses infect tissue-specific macrophages *in vivo*, and animals show low levels of viral replication. Specific neutralizing antibodies are not regularly produced in natural infection with nonlaboratory-infected strains. Mutations cause the virus to change its surface antigens, particularly of the envelope, and antigenic drift occurs in the face of antibody production [Narayan and Cork, 1985]. These phenomenon are important in the pathogenesis of chronic infections. Virus-infected sheep and goats, which have been immunosuppressed, do not develop lesions, suggesting that some of the neuropathology is the result of immunological processes. Infections of visna and goat leukoencephalomyelitis differ from the AIDS encephalopathy in that the human patients show a relative paucity of inflammatory cell response presumably related to the immunodeficiency occurring in these patients. In spite of some difference in the expression of disease, these animal models are important because they can be used to clarify pathogenetic mechanisms causing retrovirus encephalopathies and because they can be used to test new therapies that may be difficult to assess in human patients.

Visna and Goat Leukoencephalomyelitis

Clinical Manifestations. Visna, first recognized in sheep in Iceland in 1935 [Johnson, 1982], manifests as a stumbling gait and ataxia, which progresses over months to paralysis of the hind limbs. Animals are afebrile and remain alert until the late stages of disease. Goat leukoencephalomyelitis, typically presents as weakness of the hind limbs which progresses over a short interval (1-2 weeks) to quadriplegia [Cork et al., 1974a]. Affected animals are normally afebrile and alert.

Laboratory Studies. In visna virus-infection animals, the CSF contains white cells, and the levels of CSF protein are increased. In goat leukoencephalitis, there may be pleocytosis and increased protein content in CSF, but these findings are not consistent. Virus-infected animals usually develop antibodies between 1-3 months after innoculation, and antibody levels in the CSF may rise to exceed those in serum [Griffin et al., 1978]. The predominant immunoglobulin type (IgG) is presumably generated by plasma cells within the CNS and is directed against visna virus.

Neuropathology. Examination of brains of visna-infected animals disclosed mononuclear inflammation in the meninges and perivascular space, particularly in white matter [Petursson et al., 1976], with demyelination and leukomalacia in proximity to these inflammatory infiltrates. Viral antigen has been difficult to demonstrat, and ultrastructural examinations have failed to demonstrate viral particles [Narayan et al., 1974; Georggson et al., 1977]. Recently, however, using double-staining techniques, virus has been identified in oligodendrocytes [Stowring et al., 1985]. In situ hybridization studies of infected cell cultures have demonstrated that the virus is present as proviral DNA [Haase et al., 1977]. The virus infects macrophages in brain [Clements et al., 1980], has cytopathic activity resembling HTLV-III, and persists in cells in unintegrated viral DNA [Gonda et al., 1985].

Examinations of brains of goat leukoencephalomyelitis-infected animals show large numbers of macrophages, lymphocytes, and plasma cells in perivascular locations, diffusely infiltrating the neuropil and meninges [Cork et al., 1974b]. Brain lesions are multifocal, involving brain and spinal cord but are most prevalent in periventricular and subpial regions. The mildest lesions are focal accumulations of mononuclear cells, with an accompanying response of microglia and astrocytes. In these regions, myelin sheaths are destroyed, but axons are relatively preserved. In more severe lesions, there are large numbers of lymphocytes, plasma cells, and macrophages around regions of necrosis with cavitation and mineralization of adjacent tissues. Chronic lesions are associated with a loss of myelin and intense astrogliosis with relatively fewer inflammatory cells.

Pathogenetic Mechanisms. Parenchymal lesions in sheep and goats infected with lentiviruses are believed to result from interactions between viral antigens expressed on the surface of infected cells and components of the antiviral immune response of the host [Nathanson et al., 1976,1981]. These viruses replicate indefinitely at restricted levels in target tissues and are unaffected by antiviral immune responses [Narayan and Cork, 1985]. The lentivirus possesses an RNA-dependent DNA polymerase that allows integration of proviral DNA into host DNA and, thus, the unexpressed viral genome is protected from host defense mechanisms [Haase and Varmus, 1973; Adams et al., 1980]. Thus, the virus is not eliminated. High levels of IgG and inflammatory cells enlisted in the immune response cause local tissue damage. Antibodies are induced against all polypeptides of the virion, with early antibodies showing a narrow antibody spectrum, while later antibodies are directed against many epitopes. It is thought that antigenic drift provides a mechanism for escape from antibody control. Antigenic mutations of visna virus occur within persistently infected sheep [Narayan et al., 1978] and accumulate in the region of the viral genome that codes for the large-surface glycoprotein that elicits neutralizing antibody [Clements et al., 1980].

Cells of the monocyte macrophage series are hosts for replication of sheep and goat lentiviruses *in vivo*, and virus can be obtained from peripheral blood monocytes and macrophages in inflammed tissues. Infected macrophages may play a role as a vehicle of viral transmission from animal to animal as well as in individual animals and may provide a point of viral entry into the host for specific targets. In the natural disease, infectious virus may be introduced into brain by passage of affected monocytes across the blood-brain barrier, with subsequent spread of the agent into parenchymal cells (e.g., oligodendrocytes). Infected macrophages in colostrum and milk may be a method of transmitting disease to young animals in the field. Only minimal quantities of cell-free infectious virus can be obtained from infected tissues, due to the fact that most virus is present as proviral DNA [Haase et al., 1977; Narayan et al., 1977]. Exponential viral replication occurs in cell culture, and large amounts of extracellular virus can be detected. The restriction of viral replication *in vitro* appears to be due to a complex interaction whereby lentiviruses induce a factor in macrophages that stimulates lymphocytes to produce interferon. Interferon is capable of restricting viral replication [Narayan et al., in press].

Simian Acquired Immunodeficiency Syndrome

Beginning as early as 1971 [Stowell et al., 1971], there have been an increasing number of reports from primate centers within the United States concerning retroviral infections in nonhuman primates in association with a variety of neoplastic and immune deficiency diseases. When reinoculated into the host species, individual viral isolates may or may not produce disease but may do so if inoculated into another macaque species. Infection has been reported with at least three types of retroviruses: type D retroviruses [Daniel et al., 1985]; lentiviruses related to the HTLV-III group of viruses isolated from humans [Daniel et al., 1985; Kanki et al., 1985]; and a virus related to the HTLV-I virus that has been associated with leukemia in humans [Gallo et al., 1985]. The majority of these simian viruses are incompletely characterized as yet, but at least one isolate also shows serological cross reactivity wityh HTLV-III [Daniel et al., 1985]. Thus, this simian lentivirus may be potentially of benefit in studying the neurological syndromes associated with AIDS in nonhuman primates. Lentivirus-infected nonhuman primates could be used for sequential behavioral studies of cognitive functions during infection, and detailed clinicopathological/virological studies could be carried out to determine the cells at risk and the pathogenesis of infection. In addition, therapeutic strategies could be tested to examine the potential benefits and risks. Furthur studies are needed to fully characterize the simian lentiviruses and their relationship to the human retroviruses associated with AIDS, but some isolates show considerable promise as potential models for the human disease.

Treatment Strategies

To date, there is no effective therapy for the viral infection causing AIDS or symptomatic treatment for the dementia occurring in this setting. Immunomodulatory agents and lymphobines may improve T-cell function and allow the host immune system to overcome systemic opportunistic infection, but the retrovirus infection of neural cells may continue unabated [Johnson and McArthur, in press]. A variety of drugs, including HPA-23, ribavarin, ansamycin, suramin, trisodium phosphoformate, and azidothymidine, are undergoing evaluation as possible therapeutic agents. Some of these drugs do not affect proviral DNA but would interfere with the production of virus. However, to be effective in dementia, these drugs will have to cross the blood-brain barrier. If they do not cross the blood-brain barrier, the systemic infection may be cleared, but infection in the CNS will continue to destroy brain cells. Moreover, certain properties of AIDS infection (e.g., the relative lack of antibody, the ability of the virus to persist in sera containing some antibody, genetic heterogeneity of the virus, etc.) will present problems in developing effective vaccines for this infection. Clearly, the development of new chemotherapeutic applications and vaccines will be important approaches to the treatment of the AIDS-dementia complex.

CONCLUSION

As the above-outlined review makes clear, recent progress in investigations of dementia would not have been possible were it not for the multidisciplinary contributions of basic science. Sometimes, new advances have obvious and direct benefits to patients. Examples of these direct effects include the development of L-dopa for the treatment of PD and the application of imaging techniques (e.g., computerized tomography) for diagnostic studies. More frequently, the contributions of basic science are less directly apparent, and, yet, these discoveries may lead to new breakthroughs providing clues to human illness. For example, discovery of monoclonal antibodies has allowed the development of new approaches to components within neurons, and immunocytochemical techniques with some of these antibodies have defined a variety of transmitter systems in the CNS. This technology has been essential in defining the cholinergic, somatostatinergic, and CRF systems, which are known to be affected in individuals with AD. Discoveries in molecular biology have led to recombinant DNA technologies which are now being used to localize abnormal genes (e.g., the HD gene on chromosome 4) and, eventually, will be useful for cloning and characterizing a variety of CNS genes, including those implicated in disease. Techniques derived from immunology and virology have been applied to studies of neurological disease and have demonstrated the roles of unconventional viruses in CJD and retroviruses in AIDS encephalopathy. In addition, computer techniques for imaging and modeling are being used increasingly to analyze brain structure and function in living patients and in individuals with disease. Some of these approaches can be applied to animal models and to investigations of tissue obtained postmortem. New approaches derived from basic neuroscience will continue to create new opportunities for exploring ways in which disease affects the CNS. Moreover, the information and excitement created by new discoveries will continue to attract young physicians and scientists into this field who will go on to make the important discoveries of the future.

In conclusion, diseases causing dementia are a challenging group of illnesses involving the most complex of organs -- the human brain. It is difficult to predict which areas of research will produce the major advances in our knowledge of these diseases. To insure the success of this research, physicians and basic scientists must work together on the disorders leading to dementia, and society must recognize that this effort requires a major allocation of federal resources. It is certain that multidisciplinary neuroscience will be the principal source of our understanding of processes occurring in the normal and abnormal brain.

ACKNOWLEDGEMENTS

The author gratefully acknowledges helpful discussions with many colleagues at The Johns Hopkins University School of Medicine, including Drs. G.A. Alexander, M.F. Casanova, L.C. Cork, J.T. Coyle, E.B. D'Souza, M.R. DeLong, J.W. Griffin, P.N. Hoffman, R.T. Johnson, C.A. Kitt, D.L. Landstrom, J.C. McArthur, W.C. Miller, S.J. Mitchell, N.E. Rance, R.G. Struble, J.C. Troncoso, L.C. Walker, P.J. Whitehouse, and R.M. Zweig.

Many investigators (Appendix III) kindly responded to my inquiries and provided me with preprints and reprints of their work. These scientists are listed in alphabetical order: Y. Agid, A.J. Aguayo, M.S. Albert, S.H. Appel, M. Ball, R.T. Bartus, F. Benson, L. Berg, J. Blass, G. Blessed, F. Boller, D.M. Bowen, T. Budinger, D.B. Calne, A. Carlsson, P.D. Coleman, S.H. Corkin, C.W. Cotman, T. Crook, P. Davies, K.L. Davis, P.C. Emson, C.J. Epstein, M.M. Esiri, S.H. Ferris, C.E. Finch, R.S.J. Frachowiak, P. Fuld, P. Gambetti, S. Gershon, G.G. Glenner, P. Goldman-Rakic, C.G. Gottfries, J. Growdon, J.S. Gusella, L.L. Heston, A. Heyman, O. Hornykiewicz, L.L. Iversen, J. Jankovic, R.T. Johnson, E.R. Kandel, I. Karlsson, D. Kuhl, L. Kurland, J.W. Langston, R.J. Lasek, C.A. Marotta, C.D. Marsden, J.B. Martin, C. Masters, R. Mayeux, J.Z. Mazziotta, M-M. Mesulam, C.Q. Mountjoy, C.B. Nemeroff, A. Peters, T.P.S. Powell, R.W. Price, S.B. Prusiner, M. Raichle, S.I. Rapoport, T.S. Reese, M. Rossor, M. Roth, D.J. Selkoe, J.R. Sladek, Jr., I. Shoulson, L.J. Thal, S.J. Watson, Jr., N.S. Wexler, B. Winblad, H.M. Wisniewski, K. Wisniewski, S.H. Yen, A.B. Young.

LITERATURE CITED

Abelson PH, Butz E and Snyder SH: Neuroscience. Washington, D.C., The American Association for the Advancement of Science, 1985.

Adams DS, Crawford TB, Bank KL, McGuire TC and Perryman LE: Immune responses of goats persistently infected with caprine arthritis-encephalitis virus. Infect. Immun. 28: 421-427, 1980.

Adams RD and Victor M: Principles of Neurology, third edition. New York, McGraw-Hill, 1985.

Adolfsson R, Gottfries CG, Oreland L, Roos BE and Winblad B: Reduced levels of catecholamines in the brain and increased activity of monoamine oxidase in platelets in Alzheimer's disease: therapeutic implications. In: Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7). R Katzman, RD Terry and KL Bick (eds), New York, Raven Press, 1978, pp 441-451.

Agid Y and Javoy-Agid F: Peptides and Parkinson's disease. Trends Neurosci. 8: 30-35, 1985.

Aguayo A, David S, Richardson P and Bray G: Axonal elongation in peripheral and central nervous system transplants. Adv. Cell. Neurobiol. 3: 215-234, 1982.

Aigner T, Aggleton J, Mitchell SJ, Price D, DeLong M and Mishkin M: Effects of scopolamine on recognition memory in monkeys after ibotenic acid injections into the nucleus basalis of Meynert. Soc. Neurosci. Abstr. 9: 826, 1983.

Aigner T, Mitchell S, Aggleton J, DeLong M, Struble R, Wenk G, Price D and Mishkin M: Recognition deficit in monkeys following neurotoxic lesions of the basal forebrain. Soc. Neurosci. Abstr. 10: 386, 1984.

Alexander GE, DeLong MR and Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci., in press.

Alvord EC Jr: The pathology of parkinsonism. Part II. An interpretation with special reference to other changes in the aging brain. In: Recent Advances in Parkinson's Disease. FH McDowell and CH Markham (eds), Philadelphia, F.A. Davis, 1971, pp 131-161.

Anderton BH, Breinburg D, Downes MJ, Green PJ, Tomlinson BE, Ulrich J, Wood JN and Kahn J: Monoclonal antibodies show that neurofibrillary tangles and neurofilaments share antigenic determinants. Nature 298: 84-86, 1982.

Appel SH: A unifying hypothesis for the cause of amyotrophic lateral sclerosis, parkinsonism, and Alzheimer disease. Ann. Neurol. 10: 499-505, 1981.

Arendt T, Bigl V, Arendt A and Tennstedt A: Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans, and Korsakoff's disease. Acta Neuropathol. (Berl) 61: 101-108, 1983.

Aronin N, Cooper PE, Lorenz LJ, Bird ED, Sagar SM, Leeman SE and Martin JB: Somatostatin is increased in the basal ganglia in Huntington disease. Ann. Neurol. 13: 519-526, 1983.

Ball MJ, Fisman M, Hachinski V, Blume W, Fox A, Krall VA, Kirshen AJ, Fox H and Merskey H: A new definition of Alzheimer's disease: a hippocampal dementia. Lancet 1: 14-16, 1985.

Ball MJ: Neuronal loss, neurofibrillary tangles and granulovacuolar degeneration in the hippocampus with ageing and dementia. A qualitative study. Acta Neuropathol. (Berl.) 37: 111-118, 1977.

Ball MJ: The morphological basis of dementia in Parkinson's disease. Can. J. Neurol. Sci. 11: 180-184, 1984.

Ball MJ: Topographic distribution of neurofibrillary tangles and granulovacuolar degeneration in hippocampal cortex of aging and demented patients. A quantitative study. Acta Neuropathol. (Berl.) 42: 73-80, 1978.

Ballard PA, Tetrud JW and Langston JW: Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6,tetrahydropyridine (MPTP): seven cases. Neurology 35: 949-956, 1985.

Barbeau A, Roy M and Boyer L: Genetic studies in Parkinson's disease. In: Parkinson-Specific Motor and Mental Disorders. Role of the Pallidum: Pathophysiological, Biochemical, and Therapeutic Aspects. Advances in Neurology, Vol. 40. RG Hassler and JF Christ (eds), New York, Raven Press, 1984, pp 333-339.

Barde Y-A, Edgar D and Thoenen H: New neurotrophic factors. Annu. Rev. Physiol. 45: 601-612, 1983.

Baringer JR and Prusiner SB: Experimental scrapie in mice: ultrastructural observations. Ann. Neurol. 4: 205-211, 1978.

Baringer JR, Gajdusek DC, Gibbs CJ Jr, Masters CL, Stern WE and Terry RD: Transmissible dementias: current problems in tissue handling. Neurology 30: 302-303, 1980.

Baringer JR, Wong J, Klassen T and Prusiner SB: Further observations on the neuropathology of experimental scrapie in mouse and hamster. In: Pathogenesis, Immunology, Virology, and Molecular Biology of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 2. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979, pp 111-121.

Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W and Montagnier L: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220: 868-871, 1983.

Bartus RT, Fleming D and Johnson HR: Aging in the rhesus monkey: debilitating effects on short-term memory. J. Gerontol. 33: 858-871, 1978.

Beal MF, Mazurek MF, Tran VT, Chattha G, Bird ED and Martin JB: Reduced numbers of somatostatin receptors in the cerebral cortex in Alzheimer's disease. Science 229: 289-291, 1985.

Beck E and Daniel PM: Kuru and Creutzfeldt-Jakob disease: neuropathological lesions and their significance. In: Clinical, Epidemiological, Genetic, and

Pathological Aspects of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 1. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979, pp 253-270.

Beck E, Daniel PM, Matthews WB, Stevens DL, Alpers MP, Asher DM, Gajdusek DC and Gibbs CJ Jr: Creutzfeldt-Jakob disease. The neuropathology of a transmission experiment. Brain 92: 699-716, 1969.

Bendheim PE, Barry RA, DeArmond SJ, Stites DP and Prusiner SB: Antibodies to a scrapie prion protein. Nature 310: 418-421, 1984.

Bendheim PE, Bockman JM, McKinley MP, Kingsbury DT and Prusiner SB: Scrapie and Creutzfeldt-Jakob disease prion proteins share physical properties and antigenic determinants. Proc. Natl. Acad. Sci. USA 82: 997-1001, 1985.

Berg L: Does Alzheimer's disease represent an exaggeration of normal aging? Arch. Neurol. 42: 737-739, 1985.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K and Seitelberger F: Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J. Neurol. Sci. 20: 415-455, 1973.

Bernoulli C, Siegfried J, Baumgartner G, Regli F, Rabinowicz T, Gajdusek DC and Gibbs CJ Jr: Danger of accidental person-to-person transmission of Creutzfeldt-Jakob disease by surgery. Lancet 1: 478-479, 1977.

Bird ED: Chemical pathology of Huntington's disease. Annu. Rev. Pharmacol. Toxicol. 20: 533-551, 1980.

Bissette G, Nemeroff CB, Decker MW, Kizer JS, Agid Y and Javoy-Agid F: Alterations in regional brain concentrations of neurotensin and bombesin in Parkinson's disease. Ann. Neurol. 17: 324-328, 1985a.

Bissette G, Reynolds GP, Kilts CD, Widerlöv E and Nemeroff CB: Corticotropin-releasing factor (CRF)-like immunoreactivity in senile dementia of the Alzheimer type. J. A. M. A. 254: 3067-3069, 1985b.

Bizzi A, Crane RC, Autilio-Gambetti L and Gambetti P: Aluminum effect on slow axonal transport: a novel impairment of neurofilament transport. J. Neurosci. 4: 722-731, 1984.

Björklund A, Stenevi U, Schmidt RH, Dunnett SB and Gage FH: Intracerebral grafting of neuronal cell suspensions. I. Introduction and general methods of preparation. Acta Physiol. Scand. Suppl. 522: 1-7, 1983.

Black IB, Adler JE, Dreyfus CF, Jonakait GM, Katz DM, LaGamma EF and Markey DM: Neurotransmitter plasticity at the molecular level. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 30-39.

Blass JP and Zemcov A: Alzheimer disease: a metabolic systems degeneration? Neurochem. Pathol., in press.

Bockman JM, Kingsbury DT, McKinley MP, Bendheim PE and Prusiner SB: Creutzfeldt-Jakob disease prion proteins in human brains. N. Engl. J. Med. 312: 73-78, 1985.

Boller F, Mizutani T, Roessmann U and Gambetti P: Parkinson disease, dementia, and Alzheimer disease: clinicopathological correlations. Ann. Neurol. 7: 329-335, 1980.

Boller F: Parkinson's disease and Alzheimer's disease: are they associated? In: Proceedings of the Norman Rockwell Conference on Alzheimer's Disease. JT Hutton and AD Kenny (eds), New York, Alan R. Liss, Inc., in press.

Bolton DC, McKinley MP and Prusiner SB: Identification of a protein that purifies with the scrapie prion. Science 218: 1309-1311, 1982.

Bolton DC, Meyer RK and Prusiner SB: Scrapie PrP 27-30 is a sialoglycoprotein. J. Virol. 53: 596-606, 1985.

Bondareff W, Mountjoy CQ and Roth M: Loss of neurons or origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. Neurology 32: 164-168, 1982.

Bowen DM, Allen SJ, Benton JS, Goodhardt MJ, Haan EA, Palmer AM, Sims NR, Smith CCT, Spillane JA, Esiri MM, Neary D, Snowdon JS, Wilcock GK and Davison AN: Biochemical assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. J. Neurochem. 41: 266-272, 1983.

Bowen DM, Smith CB, White P and Davison AN: Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain 99: 459-496, 1976.

Brown P, Gajdusek DC, Gibbs CJ Jr and Asher DM: Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N. Engl. J. Med. 313: 728-731, 1985.

Bruyn GW: Huntington's chorea. Historical, clinical and laboratory synposis. In: Diseases of the Basal Ganglia, Handbook of Clinical Neurology, Vol. 6. PJ Vinken and GW Bruyn (eds), Amsterdam, North-Holland Publishing Co., 1968, pp 298-378.

Buell SJ and Coleman PD: Quantitative evidence for selective dendritic growth in normal human aging but not in senile dementia. Brain Res. 214: 23-41, 1981.

Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM and Kopin IJ: A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc. Natl. Acad. Sci. USA 80: 4546-4550, 1983.

Bustany P, Henry JF, Soussaline F and Comar D: Brain protein synthesis in normal and demented patients -- a study by positron emission tomography with ^{11}C-L-methionine. In: Functional Radionuclide Imaging of the Brain. Serono Symposia, Vol. 5. PL Magistretti (ed), New York, Raven Press, 1983, pp 319-326.

Calne DB and Langston JW: Aetiology of Parkinson's disease. Lancet 2: 1457-1459, 1983.

Calne DB, Duvoisin RC and McGeer E: Speculations on the etiology of Parkinson's disease. In: Parkinson-Specific Motor and Mental Disorders. Role of the Pallidum: Pathophysiological, Biochemical, and Therapeutic Aspects. Advances in Neurology, Vol. 40. RG Hassler and JF Christ (eds), New York, Raven Press, 1984, pp 353-360.

Candy JM, Perry RH, Perry EK, Irving D, Blessed G, Fairbairn AF and Tomlinson BE: Pathological changes in the nucleus of Meynert in Alzheimer's and Parkinson's diseases. J. Neurol. Sci. 59: 277-289, 1983.

Carlsson A and Winblad B: Influence of age and time interval between death and autopsy on dopamine and 3-methoxy-tyramine levels in human basal ganglia. J. Neural Transm. 38: 271-276, 1976.

Casanova MF, Walker LC, Whitehouse PJ and Price DL: Abnormalities of the nucleus basalis in Down's syndrome. Ann. Neurol. 18: 310-313, 1985.

Catterall WA: The molecular basis of neuronal excitability. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 248-265.

Changeux J-P, Devillers-Thiéry A and Chemouilli P: Acetylcholine receptor: an allosteric protein. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 216-238.

Clark AW, Parhad IM, Folstein SE, Whitehouse PJ, Hedreen JC, Price DL and Chase GA: The nucleus basalis in Huntington's disease. Neurology 33: 1262-1267, 1983.

Clements JE, Narayan O and Cork LC: Biochemical characterization of goat leukoencephalitis virus. J. Gen. Virol. 50: 423-427, 1980.

Colon EJ: The cerebral cortex in presenil dementia. A quantitative analysis. Acta Neuropathol. (Berl.) 23: 281-290, 1973.

Cork LC, Hadlow WJ, Crawford TB, Gorham JR and Piper RC: Infectious leukoencephalomyelitis of young goats. J. Infect. Dis. 129: 134-141, 1974a.

Cork LC, Hadlow WJ, Gorham JR, Piper RC and Crawford TB: Pathology of viral leukoencephalomyelitis of goats. Acta Neuropathol. (Berl.) 29: 281-292, 1974b.

Cork LC, Sternberger NH, Sternberger LA, Casanova MF, Struble RG and Price DL: Phosphorylated neurofilament antigens in neurofibrillary tangles in Alzheimer's disease. J. Neuropathol. Exp. Neurol. 45: 56-64, 1986.

Corsellis JAN: Posttraumatic dementia. In: Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7). R Katzman, RD Terry and KL Bick (eds), New York, Raven Press, 1978, pp 125-133.

Cotman CW and Nieto-Sampedro M: Cell biology of synaptic plasticity. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 74-88.

Coyle JT and Schwarcz R: Model for Huntington's chorea: lesion of striatal neurons with kainic acid. Nature 263: 244-246, 1976.

Crapper DR, Karlik S and DeBoni U: Aluminum and other metals in senile (Alzheimer) dementia. In: Alzheimer's Disease: Senile Dementia and Related

Disorders (Aging, Vol. 7). R Katzman, RD Terry and KL Bick (eds), New York, Raven Press, 1978, pp 471-485.

Crapper DR, Krishnan SS and Dalton AJ: Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 180: 511-513, 1973.

Crapper DR, Quittkat S and DeBoni U: Altered chromatin conformation in Alzheimer's disease. Brain 102: 483-495, 1979.

Cross AJ, Crow TJ, Perry EK, Perry RH, Blessed G and Tomlinson BE: Reduced dopamine-β-hydroxylase activity in Alzheimer's disease. Br. Med. J. 282: 93-94, 1981.

Curcio CA and Kemper T: Nucleus raphe dorsalis in dementia of the Alzheimer type: neurofibrillary changes and neuronal packing density. J. Neuropathol. Exp. Neurol. 43: 359-368, 1984.

Curran JW, Morgan WM, Hardy AM, Jaffe HW, Darrow WW and Dowdle WR: The epidemiology of AIDS: current status and future prospects. Science 229: 1352-1357, 1985.

Daniel MD, Letvin NL, King NW, Kannagi M, Sehgal PK, Hunt RD, Kanki PJ, Essex M and Desrosiers RC: Isolation of T-cell tropic HTLV-III-like retrovirus from macaques. Science 228: 1201-1204, 1985.

Davies P and Maloney AJF: Selective loss of central cholinergic neurons in Alzheimer senile dementia. Nature 288: 279-280, 1976.

Davies P, Katzman R and Terry RD: Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementia. Nature 288: 279-280, 1980.

Davis GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM and Kopin IJ: Chronic parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res. 1: 249-254, 1979.

Davis RT: Old monkey behavior. Exp. Gerontol. 13: 237-250, 1978.

Davis RT: The effects of aging on the behavior of rhesus monkeys. In: Behavior and Pathology of Aging in Rhesus Monkeys, Monographs in Primatology, Vol. 8. RT Davis and CW Leathers (eds), New York, Alan R. Liss, 1985, pp 57-82.

DeArmond SJ, McKinley MP, Barry RA, Braunfeld MB, McColloch JR and Prusiner SB: Identification of prion amyloid filaments in scrapie-infected brain. Cell 41: 221-235, 1985.

DeSouza EB, Whitehouse PJ, Kuhar MJ, Price DL and Vale WW: Reciprocal changes in corticotropin-releasing factor (CRF)-like immunoreactivity and CRF receptors in cerebral cortex of Alzheimer's disease. Nature 319: 593-595, 1986.

Dickinson AG and Fraser H: An assessment of the genetics of scrapie in sheep and mice. In: Clinical, Epidemiological, Genetic, and Pathological Aspects of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 1. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979, pp 367-385.

Dickinson AG, Bruce ME and Scott JR: The relevance of scrapie as an experimental model for Alzheimer's disease. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 387-398, 1983.

Divac I: The neostriatum veiwed orthogonally. In: Functions of the Basal Ganglia. Ciba Foundation Symposium 107. London, Pitman, 1984, pp 201-215.

Drachman DA and Stahl S: Extrapyramidal dementia and levodopa. Lancet 1: 809, 1975.

Duckett S and Galle P: Microscopie electronique biologique -- mise en evidence de l'aluminum dans les plaques seniles de la maladie d'Alzheimer: etude a la microsonde de Castaing. C. R. Soc. Biol. (Paris) 282: 393-395, 1976.

Duffy P, Wolf J, Collins G, DeVoe AG, Streeten B and Cowen D: Possible person-to-person transmission of Creutzfeldt-Jakob disease. N. Engl. J. Med. 290: 692-693, 1984.

Dunnett SB, Björklund A and Stenevi U: Dopamine-rich transplants in experimental parkinsonism. Trends Neurosci. 6: 266-270, 1983.

Duvoisin RC and Yahr MD: Encephalitis and parkinsonism. Arch. Neurol. 12: 227-239, 1965.

Duvoisin RC: The cause of Parkinson's disease. In: Movement Disorders, Neurology, Vol. 2. CD Marsden and S Fahn (eds), London, Butterworth Scientific, 1982, pp 8-24.

Eldridge R and Ince SE: The low concordance rate for Parkinson's disease in twins: a possible explanation. Neurology 34: 1354-1356, 1984.

Eldridge R, Rocca WA and Ince SE: Parkinson's disease: evidence against a toxic etiology and for an alternative theory. In: MPTP -- A Neurotoxin Producing A Parkinsonian Syndrome. SP Markey, N Castagnoli Jr, AJ Trevor and IJ Kopin (eds), New York, Academic Press, in press.

Emson PC, Arregui A, Clement-Jones V, Sandberg BEB and Rossor M: Regional distribution of methionine-enkephalin and substance P-like immunoreactivity in normal human brain and in Huntington's disease. Brain Res. 199: 147-160, 1980.

Emson PC: Chemical Neuroanatomy. New York, Raven Press, 1983.

Epelbaum J, Ruberg M, Moyse E, Javoy-Agid F, Dubois B and Agid Y: Somatostatin and dementia in Parkinson's disease. Brain Res. 278: 376-379, 1983.

Epstein LG, Sharer LR, Cho E-S, Meyenhofer M, Navia BA and Price RW: HTLV-III/LAV-like retrovirus particles in the brains of patients with AIDS encephalopathy. AIDS Res. 1: 447-454, 1985a.

Epstein LG, Sharer LR, Joshi VV, Fojas MM, Koenigsberger MR and Oleske JM: Progressive encephalopathy in children with acquired immune deficiency syndrome. Ann. Neurol. 17: 488-496, 1985b.

Evarts EV: Brain mechanisms of movement. Sci. Am. 241: 164-179, 1979.

Ferrier IN, Cross AJ, Johnson JA, Roberts GW, Crow TJ, Corsellis JAN, Lee YC, O'Shaughnessy D, Adrian TE, McGregor GP, Baracese-Hamilton AJ and Bloom SR: Neuropeptides in Alzheimer type dementia. J. Neurol. Sci. 62: 159-170, 1983.

Folstein M, Anthony JC, Parhad I, Duffy B and Gruenberg EM: The meaning of cognitive impairment in the elderly. J. Am. Geriatr. Soc. 33: 228-235, 1985.

Folstein MF and Breitner JCS: Language disorder predicts familial Alzheimer's disease. Johns Hopkins Med. J. 149: 145-147, 1981.

Folstein MF and Powell D: Is Alzheimer disease inherited: a methodological review. Integrat. Psychiatry 2: 1984.

Folstein SE and Folstein MF: Psychiatric features of Huntington disease: recent approaches and findings. Psychiatr. Dev. 2: 193-206, 1983.

Folstein SE, Abbott MH, Chase GA, Jensen B and Folstein MF: The association of affective disorder with Huntington's disease in the case series and in families. Psychol. Med. 13: 537-542, 1983.

Forno LS: Pathology of Parkinson's disease. In: Movement Disorders, Neurology, Vol. 2. CD Marsden and S Fahn (eds), London, Butterworth Scientific, 1982, pp 25-40.

Foster NL, Chase TN, Fedio P, Patronas NJ, Brooks RA and DiChiro G: Alzheimer's disease: focal cortical changes shown by positron emission tomography. Neurology 33: 961-965, 1983.

Foster NL, Chase TN, Mansi L, Brooks R, Fedio P, Patronas NJ and DiChiro G: Cortical abnormalities in Alzheimer's disease. Ann. Neurol. 16: 649-654, 1984.

Frackowiak RSJ and Gibbs JM: The pathophysiology of Alzheimer's disease studied with positron emission tomography. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 317-327, 1983.

Frackowiak RSJ and Gibbs JM: Vascular dementia. Observations from positron emission tomography. In: Proceedings of Submeeting on Brain and Hypotension. A Bés and G Geraud (eds), Paris, Masson, in press.

Frackowiak RSJ: Measurement and imaging of cerebral function in ageing and dementia: a review. Prog. Brain Res., in press.

Francis PT, Palmer AM, Sims NR, Bowen DM, Davison AN, Esiri MM, Neary D, Snowden JS and Wilcock GK: Neurochemical studies of early-onset Alzheimer's disease. Possible influence on treatment. N. Engl. J. Med. 313: 7-11, 1985.

Friedland RP, Budinger TF, Brant-Zawadzki M and Jagust WJ: The diagnosis of Alzheimer-type dementia. A preliminary comparison of positron emission tomography and proton magnetic resonance. J. A. M. A. 252: 2750-2752, 1984.

Friedland RP, Budinger TF, Ganz E, Yano Y, Mathis CA, Koss B, Ober BA, Huesman RH and Derenzo SE: Regional cerebral metabolic alterations in dementia of the Alzheimer type: positron emission tomography with [^{18}F]fluorodeoxyglucose. J. Comput. Assist. Tomogr. 7: 590-598, 1983.

Gado M, Hughes CP, Danziger W and Chi D: Aging, dementia, and brain atrophy: a longitudinal computed tomographic study. Am. J. Neuroradiol. 4: 699-702, 1983.

Gage FH, Dunnett SB, Stenevi U and Björklund A: Aged rats: recovery of motor impairments by intrastriatal nigral grafts. Science 221: 966-969, 1983.

Gajdusek DC and Zigas V: Kuru. Clinical, pathological and epidemiological study of an acute progressive degenerative disease of the central nervous system among natives of the Eastern Highlands of New Guinea. Am. J. Med. 26: 442-469, 1959.

Gajdusek DC, Amyx HL, Gibbs CJ Jr, Asher DM, Rodgers-Johnson P, Epstein LG, Sarin PS, Gallo RC, Maluish A, Gilden RV, Arthur OL, Montagnier L and Mildvan D: Infection of chimpanzees by human T-lymphotrophic retroviruses in brain and other tissues from AIDS patients. Lancet 1: 55-56, 1985.

Gajdusek DC, Gibbs CJ Jr, Asher DM, Brown P, Diwan A, Hoffman P, Nemo G, Rohwer R and White L: Precautions in medical care of, and in handling materials from, patients with transmissible virus dementia (Creutzfeldt-Jakob disease). N. Engl. J. Med. 297: 1253-1258, 1977.

Gajdusek DC: Interference with axonal transport of neurofilament as the common etiology and pathogenesis of neurofibrillary tangles, amyotrophic lateral sclerosis, parkinsonism-dementia, and many other degenerations of the CNS: a series of hypotheses (Perspectives for Research). In: Amyotrophic Lateral

Sclerosis in Asia and Oceania. KM Chen and Y Yase (eds), Taiwan, Shyan-Fu Chou, 1984a, pp 423-436.

Gajdusek DC: Subacute spongiform virus encephalopathies caused by unconventional viruses. In: Subviral Pathogens of Plants and Animals: Viroids and Prions. K Maramorosch and JJ McKelvey Jr (eds), New York, Academic Press, 1985a, pp 483-544.

Gajdusek DC: Unconventional viruses causing subacute spongiform encephalopathies. In: Virology. BN Fields et al. (eds), New York, Raven Press, 1985b, pp 1519-1557.

Gajdusek DC: Unconventional viruses. In: Concepts in Viral Pathogenesis. AL Notkins and MBA Oldstone (eds), New York, Springer-Verlag, 1984b, pp 350-357.

Gale JS, Bird ED, Spokes EG, Iversen LL and Jessell T: Human brain substance P: distribution in controls and Huntington's chorea. J. Neurochem. 30: 633-634, 1978.

Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, White G, Foster P and Markham PD: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224: 500-503, 1984.

Gambetti P, Shecket G, Ghetti B, Hirano A and Dahl D: Neurofibrillary changes in human brain. An immunocytochemical study with a neurofilament antiserum. J. Neuropathol. Exp. Neurol. 42: 69-79, 1983.

Gash DM, Collier TJ and Sladek JR Jr: Neural transplantation: a review of recent developments and potential applications to the aged brain. Neurobiol. Aging 6: 131150, 1985.

Gath I, Jörgensen A, Sjaastad O and Berstad J: Pneumoencephalographic findings in parkinsonism. Arch. Neurol. 32: 769-773, 1975.

Geddes JW, Monaghan DT, Cotman CW, Lott IT, Kim RC and Chui HC: Plasticity of hippocampal circuitry in Alzheimer's disease. Science, in press.

Georgsson G, Palsson PA, Panitch H, Nathanson N and Petursson G: The ultrastructure of early visna lesions. Acta Neuropathol. (Berl.) 37: 127-135, 1977.

Gibbs CJ Jr, Joy A, Heffner R, Franko M, Miyazaki M, Asher DM, Parisi JE, Brown PW and Gajdusek DC: Clinical and pathological features and laboratory confirmation of Creutzfeldt-Jakob disease in a recipient of pituitary-derived human growth hormone. N. Engl. J. Med. 313: 734-738, 1985.

Gibson PH and Tomlinson BE: Numbers of Hirano bodies in the hippocampus of normal and demented people with Alzheimer's disease. J. Neurol. Sci. 33: 199-206, 1977.

Glenner GG and Wong CW: Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem. Biophys. Res. Commun. 120: 885-890, 1984.

Glenner GG, Henry JM and Fujihara S: Congophilic angiopathy in the pathogenesis of Alzheimer's degeneration. Ann. Pathol. 1: 105-108, 1981.

Glenner GG: Alzheimer's disease: multiple cerebral amyloidosis. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 137-144, 1983a.

Glenner GG: Alzheimer's disease. The commonest form of amyloidosis. Arch. Pathol. Lab. Med. 107: 281-282, 1983b.

Gnahn H, Hefti F, Heumann R, Schwab ME and Thoenen H: NGF-mediated increase of choline acetyltransferase (ChAT) in the neonatal rat forebrain: evidence for a physiological role of NGF in the brain? Dev. Brain Res. 9: 45-52, 1983.

Goldman JE: The association of actin with Hirano bodies. J. Neuropathol. Exp. Neurol. 42: 146-152, 1983.

Gonatas NK and Gambetti P: The pathology of the synapse in Alzheimer's disease. In: Alzheimer's Disease and Related Conditions. A Ciba Foundation Symposium. GEW Wolstenholme and M O'Connor (eds), London, Churchill, 1970, pp 169-183.

Gonatas NK, Anderson W and Evangelista I: The contribution of altered synapses in the senile plaque: an electron microscopic study in Alzheimer's dementia. J. Neuropathol. Exp. Neurol. 26: 25-39, 1967.

Gonda MA, Wong-Staal F, Gallo RC, Clements JE, Narayan O and Gilden RV: Sequence homology and morphologic similarity of HTLV-III and visna virus, a pathogenic lentivirus. Science 227: 173-177, 1985.

Goudsmit J, Morrow CH, Asher DM, Yangihara RT, Masters CL, Gibbs CJ Jr and Gajdusek DC: Evidence for and against the transmissibility of Alzheimer disease. Neurology 30: 945-950, 1980.

Graveland GA, Williams RS and DiFiglia M: Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science 227: 770-773, 1985.

Greenamyre JT, Penney JB, Young AB, D'Amato CJ, Hicks SP and Shoulson I: Alterations in L-glutamate binding in Alzheimer's and Huntington's diseases. Science 227: 1496-1499, 1985.

Griffin DE, Narayan O and Adams RJ: Early immune responses in Visna -- a slow viral infection of sheep. J. Infec. Dis. 138: 340-349, 1978.

Griffin JW, Price DL and Hoffman PN: Neurotoxic probes of the axonal cytoskeleton. Trends Neurosci. 6: 490-495, 1983.

Gusella JF, Tanzi RE, Anderson MA, Hobbs W, Gibbons K, Raschtchian R, Gilliam TC, Wallace MR, Wexler NS and Conneally PM: DNA markers for nervous system diseases. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 184-196.

Gusella JF, Tanzi RE, Anderson MA, Hobbs W, Gibbons K, Raschtchian R, Gilliam TC, Wallace MR, Wexler NS and Conneally PM: DNA markers for nervous system diseases. Science 225: 1320-1326, 1984.

Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, Young AB, Shoulson I, Bonilla E and Martin JB: A polymorphic DNA marker genetically linked to Huntington's disease. Nature 306: 234-238, 1983.

Gusella JF: Genetic linkage of the Huntington's disease gene to a DNA marker. Can. J. Neurol. Sci. 11: 421-425, 1984.

Haase AT and Varmus HE: Demonstration of a DNA provirus in the lytic growth of visna virus. Nature New Biol. 245: 237-239, 1973.

Haase AT, Stowring L, Narayan O, Griffin D and Price D: Slow persistent infection caused by visna virus: the role of host restriction. Science 195: 175-176, 1977.

Haase GR: Diseases presenting as dementia. In: Dementia, Edition 2, Contemporary Neurology Series. CE Wells (ed), Philadelphia, F.A. Davis, 1977, pp 27-67.

Hadlow WJ: Scrapie and kuru. Lancet 2: 289-290, 1959.

Hadlow WJ, Race RE, Kennedy RC and Eklund CM: Natural infection of sheep with scrapie virus. In: Pathogenesis, Immunology, Virology, and Molecular Biology of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 2. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979, pp 3-12.

Hakim AM and Mathieson G: Dementia in Parkinson disease: a neuropathologic study. Neurology 29: 1209-1214, 1979.

Hamburger V and Oppenheim RW: Naturally occurring neuronal death in vertebrates. Neurosci. Comment. 1: 39-55, 1982.

Haxby JV, Duara R, Grady CL, Cutler NR and Rapoport SI: Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. J. Cereb. Blood Flow Metab. 5: 193-200, 1985.

Hedreen JC, Struble RG, Whitehouse PJ and Price DL: Topography of the magnocellular basal forebrain system in human brain. J. Neuropathol. Exp. Neurol. 43: 1-21, 1984.

Herzog AG and Kemper TL: Amygdaloid changes in aging and dementia. Arch. Neurol. 37: 625-629, 1980.

Heston LL, Mastri AR, Anderson VE and White J: Dementia of the Alzheimer type. Clinical genetics, natural history, and associated conditions. Arch. Gen. Psychiatry 38: 1085-1090, 1981.

Heston LL, McGue M and White J: Genetic relationships in early onset Alzheimer's dementia. Ann. Int. Med., in press.

Heston LL: Dementia of the Alzheimer type: a perspective from family studies. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 183-191, 1983.

Heyman A, Wilkinson WE, Hurwitz BJ, Schmechel D, Sigmon AH, Weinberg T, Helms MJ and Swift M: Alzheimer's disease: genetic aspects and associated clinical disorders. Ann. Neurol. 14: 507-515, 1983.

Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH and Weinberg T: Alzheimer's disease: a study of epidemiological aspects. Ann. Neurol. 15: 335-341, 1984.

Hirano A and Zimmerman HM: Alzheimer's neurofibrillary changes. A topographic study. Arch. Neurol. 7: 227-242, 1962.

Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, Resnick L, Felsenstein D, Andrews CA and Hirsch MS: Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N. Engl. J. Med. 313: 1493-1497, 1985.

Hoffman PN and Lasek RJ: The slow component of axonal transport. Identification of major structural polypeptides of the axon and their generality among mammalian neurons. J. Cell Biol. 66: 351-366, 1975.

Hoffman PN, Griffin JW, Gold BG and Price DL: Slowing of neurofilament transport and the radial growth of developing nerve fibers. J. Neurosci. 5: 2920-2929, 1985a.

Hoffman PN, Thompson GW, Griffin JW and Price DL: Changes in neurofilament transport coincide temporally with alterations in the caliber of axons in regenerating motor fibers. J. Cell Biol. 101: 1332-1340, 1985b.

Hökfelt T, Johansson O and Goldstein M: Chemical anatomy of the brain. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 199-215.

Hornykiewicz O: Brain neurotransmitter changes in Parkinson's disease. In: Movement Disorders, Neurology, Vol. 2. CD Marsden and S Fahn (eds), London, Butterworth Scientific, 1982, pp 41-58.

Horvitz HR, Ellis HM and Sternberg PW: Programmed cell death in nematode development. Neurosci. Comment. 1: 56-65, 1982.

Hubel DH and Wiesel TN: Brain mechanisms of vision. Sci. Am. 241: 150-162, 1979.

Hubel DH: The brain. Sci. Am. 241: 44-53, 1979.

Hubbard BM and Anderson JM: A quantitative study of cerebral atrophy in old age and senile dementia. J. Neurol. Sci. 50: 135-145, 1981.

Hyman BT, Van Hoesen GW, Damasio AR and Barnes CL: Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 225: 1168-1170, 1984.

Ihara Y, Abraham C and Selkoe DJ: Antibodies to paired helical filaments in Alzheimer's disease do not recognize normal brain proteins. Nature 304: 727-730, 1983.

Ingvar DH and Lassen NA: Activity distribution in the cerebral cortex in organic dementia as revealed by measurements of regional cerebral blood flow. In: Bayer-Symposium VII, Brain Function in Old Age, Evaluation of Changes and Disorders. F Hoffmeister and C Muller (eds), Berlin, Springer-Verlag, 1979, pp 268-277.

Iversen LL, Rossor MN, Reynolds GP, Hills R, Roth M, Mountjoy CQ, Foote SL, Morrison JH and Bloom FE: Loss of pigmented dopamine-ß-hydroxylase positive cells from locus coeruleus in senile dementia of Alzheimer's type. Neurosci. Lett. 39: 95-100, 1983.

Iversen LL: The chemistry of the brain. Sci. Am. 241: 134-149, 1979.

Jamada M and Mehraein P: Vertielungsmuster der senilen Veranderungen im Gehirn. Die Beteiligung des limbischen Systems bei hirnatrophischen Prozessen des Seniums und bei Morbus Alzheimer. Arch. Psychiatr. Z. Neurol. 211: 308-324, 1968.

Javitch JA, D'Amato RJ, Strittmatter SM and Snyder SH: Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6,tetrahydropyridine: uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity. Proc. Natl. Acad. Sci. USA 82: 2173-2177, 1985.

Javoy-Agid F and Agid Y: Is the mesocortical dopaminergic system involved in Parkinson's disease? Neurology 30: 1326-1330, 1980.

Javoy-Agid F, Ruberg M, Pique L, Bertagna X, Taquet H, Studler JM, Cesselin F, Epelbaum J and Agid Y: Biochemistry of the hypothalamus in Parkinson's disease. Neurology 34: 672-675, 1984.

Jervis GA: Early senile dementia in mongoloid idiocy. Am. J. Psychiatry 105: 102-106, 1948.

Johnson RT and McArthur JC: AIDS and the brain. Trends Neurosci., in press.

Johnson RT: Viral Infections of the Nervous System. New York, Raven Press, 1982.

Jordan BD, Navia BA, Petito CK, Cho E-S and Price RW: Neurological syndromes complicating AIDS. Front. Radiat. Ther. Oncol. 19: 82, 1985.

Jorm AF: Subtypes of Alzheimer's dementia: a conceptual analysis and critical review. Psychol. Med. 15: 543-553, 1985.

Kandel ER and Schwartz JH: Molecular biology of learning: modulation of transmitter release. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985a, pp 381-402.

Kandel ER and Schwartz JH: Principles of Neural Science, second edition. New York, Elsevier, 1985b.

Kandel ER: Small systems of neurons. Sci. Am. 241: 66-76, 1979.

Kanki PJ, Alroy J and Essex M: Isolation of T-lymphocyte retrovirus related to HTLV-III/LAV from wild-caught African Green monkeys. Science 230: 951-954, 1985.

Kascsak RJ, Rubenstein R, Merz PA, Carp RI, Wisniewski HM and Diringer H: Biochemical differences among scrapie-associated fibrils support the biological diversity of scrapie agents. J. Gen. Virol. 66: 1715-1722, 1985.

Kemper TL: Organization of the neuropathology of the amygdala in Alzheimer's disease. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 31-35, 1983.

Kemper TL: Senile dementia: a focal disease in the temporal lobe. In: Senile Dementia: A Biomedical Approach. Developments in Neuroscience, Vol. 3. K Nandy (ed), New York, Elsevier North-Holland Biomedical Press, 1978, pp 105-113.

Kidd M: Alzheimer's disease -- an electron microscopical study. Brain 87: 307-320, 1964.

Kidd M: Paired helical filaments in electron microscopy of Alzheimer's disease. Nature 197: 192-193, 1963.

Kilpatrick C, Burns R and Blumbergs PC: Identical twins with Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 46: 421-425, 1983.

Kitt CA, Cork LC, Eidelberg E, Joh TH and Price DL: Injury of nigral neurons with 1-methyl-4-phenyl-1,2,3,6,tetrahydropyridine (MPTP): a tyrosine hydroxylase immunocytochemical study in monkey. Neuroscience, in press.

Kitt CA, Price DL, Struble RG, Cork LC, Wainer BH, Becher MW and Mobley WC: Evidence for cholinergic neurites in senile plaques. Science 226: 1443-1445, 1984.

Kitt CA, Struble RG, Cork LC, Mobley WC, Walker LC, Joh TH and Price DL: Catecholaminergic neurites in senile plaques in prefrontal cortex of aged nonhuman primates. Neuroscience 16: 691-699, 1985.

Klatzo I, Wisniewski H and Streicher E: Experimental production of neurofibrillary degeneration. I. Light microscopic observations. J. Neuropathol. Exp. Neurol. 24: 187-199, 1965.

Koch TK, Berg BO, DeArmond SJ and Gravina RF: Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism: possible relation to the administration of cadaveric human growth hormone. N. Engl. J. Med. 313: 731-733, 1985.

Kosik KS, Duffy LK, Dowling MM, Abraham C, McCluskey A and Selkoe DJ: Microtubule-associated protein 2: monoclonal antibodies demonstrate the selective incorporation of certain epitopes into Alzheimer neurofibrillary tangles. Proc. Natl. Acad. Sci. USA 81: 7941-7945, 1984.

Kosik KS, Joachim C and Selkoe DJ: Tau protein is a major antigenic component of paired helical filaments. Trans. Am. Soc. Neurochem., in press.

Kretzschmar HA, Prusiner SB, Stowring LE and DeArmond SJ: Scrapie prion proteins are synthesized in neurons. Am. J. Pathol. 122: 1-5, 1986.

Kuhar MJ, DeSouza EB and Unnerstall JR: Neurotransmitter receptor mapping by autoradiography and other methods. Annu. Rev. Neurosci. 9: 27-59, 1986.

Kuhl DE, Markham CH, Metter EJ, Riege WH, Phelps ME and Mazziotta JC: Local cerebral glucose utilization in symptomatic and presymptomatic Huntington's disease. In: Brain Imaging and Brain Function. L Sokoloff (ed), New York, Raven Press, 1985a, pp 199-209.

Kuhl DE, Metter EJ and Riege WH: Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [^{18}F]fluorodeoxyglucose method. Ann. Neurol. 15: 419-424, 1984.

Kuhl DE, Metter EJ, Riege WH and Hawkins RA: Determinations of cerebral glucose utilization in dementia using positron emission tomography. Dan. Med. Bull. 32 (Suppl. 1): 51-55, 1985b.

Kuhl DE, Phelps ME, Markham CH, Metter EJ, Reige WH and Winter J: Cerebral metabolism and atrophy in Huntington's disease determined by ^{18}FDG and computer tomographic scan. Ann. Neurol. 12: 425-434, 1982.

Lane HC, Depper JM, Greene WC, Whalen G, Waldmann TA and Fauci AS: Qualitative analysis of immune function in patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. 313: 79-84, 1985.

Lange H, Thorner G, Hopf A and Schroder KF: Morphometric studies of the neuropathological changes in choreatic diseases. J. Neurol. Sci. 28: 401-425, 1976.

Lange HW: Quantitative changes of telencephalon, diencephalon, and mesencephalon in Huntington's chorea, postencephalitic, and idiopathic parkinsonism. Vehr. Anat. Ges. 75: 923-925, 1981.

Langston JW, Forno LS, Rebert CS and Irwin I: Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey. Brain Res. 292: 390-394, 1984a.

Langston JW, Irwin I, Langston EB and Forno LS: 1-Methyl-4-phenylpyridinium ion (MPP+): identification of a metabolite of MPTP, a toxin selective to the substantia nigra. Neurosci. Lett. 48: 87-92, 1984b.

Langston JW: MPTP and Parkinson's disease. Trends Neurosci. 8: 79-83, 1985.

Levi-Montalcini R and Angeletti PU: Nerve growth factor. Physiol. Rev. 48: 534-569, 1968.

Levy JA, Shimabukuro J, Hollander H, Mills J and Kaminsky L: Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. Lancet 2: 586-588, 1985.

Lieberman A, Dziatolowsky M, Kupersmith M, Serby M, Goodgold A, Korein J and Goldstein M: Dementia in Parkinson disease. Ann. Neurol. 6: 355-359, 1979.

Lott IT: Down's syndrome, aging, and Alzheimer's disease: a clinical review. Ann. N. Y. Acad. Sci. 396: 15-27, 1982.

Malamud N: Creutzfeldt-Jakob disease: a clinicopathological study. In: Clinical, Epidemiological, Genetic, and Pathological Aspects of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 1. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979, pp 271-285.

Mandybur TI: The incidence of cerebral amyloid angiopathy in Alzheimer's disease. Neurology 25: 120-126, 1975.

Mann DMA, Yates PO and Marcyniuk B: Some morphometric observations on the cerebral cortex and hippocampus in presenile Alzheimer's disease, senile dementia of Alzheimer type and Down's syndrome in middle age. J. Neurol. Sci. 69: 139-159, 1985.

Markham CH, Treciokas LJ and Diamond SG: Parkinson's disease and levodopa. A 5-year follow-up and review. West. J. Med. 121: 188-206, 1974.

Markesbery WR, Ehmann WD, Hossain TIM, Alauddin M and Goodin DT: Instrumental neutron activation analysis of brain aluminum in Alzheimer disease and aging. Ann. Neurol. 10: 511-516, 1981.

Marsden CD and Fahn S: Movement Disorders, Neurology, Vol. 2. London, Butterworth Scientific, 1982.

Marsden CD: Neurotransmitters and CNS disease. Lancet 2: 1141-1146, 1982.

Martin JB: Huntington's disease: new approaches to an old problem. Neurology 34: 1059-1072, 1984.

Mash DC, Flynn DD and Potter LT: Loss of M2 muscarine receptors in the cerebral cortex in Alzheimer's disease and experimental cholinergic denervation. Science 228: 1115-1117, 1985.

Masters CL, Gajdusek DC and Gibbs CJ Jr: Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Sträussler syndrome. With an analysis of the various forms of amyloid plaque deposition in the virus-induced spongiform encephalopathies. Brain 104: 559-588, 1981a.

Masters CL, Gajdusek DC and Gibbs CJ Jr: The familial occurrence of Creutzfeldt-Jakob disease and Alzheimer's disease. Brain 104: 535-558, 1981b.

Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C and Asher DM: Creutzfeldt-Jakob disease: patterns of worldwide occurrence. In: Clinical, Epidemiological, Genetic, and Pathological Aspects of the Spongiform Encephalopathies. Slow Transmissible Diseases of the Nervous System, Vol. 1. SB Prusiner and WJ Hadlow (eds), New York, Academic Press, 1979a, pp 113-142.

Masters CL, Harris JO, Gadjusek DC, Gibbs CJ Jr, Bernoulli C and Asher DM: Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann. Neurol. 5: 177-188, 1979b.

Masters CL, Multhaup G, Simms G, Pottgiesser J, Martins RN and Beyreuther K: Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. EMBO J., in press.

Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL and Beyreuther K: Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc. Natl. Acad. Sci. USA 82: 4245-4249, 1985.

Mayeux R and Stern Y: Intellectual dysfunction and dementia in Parkinson disease. In: The Dementias. Advances in Neurology, Vol. 38. R Mayeux and WG Rosen (eds), New York, Raven Press, 1983, pp 211-227.

Mayeux R, Stern Y and Spanton S: Heterogeneity in dementia of the Alzheimer type: evidence of subgroups. Neurology 35: 453-461, 1985.

Mayeux R, Stern Y, Rosen J and Leventhal J: Depression, intellectual impairment, and Parkinson disease. Neurology 31: 645-650, 1981.

Mayeux R: Depression and dementia in Parkinson's disease. In: Movement Disorders, Neurology, Vol. 2. CD Marsden and S Fahn (eds), London, Butterworth Scientific, 1982, pp 75-95.

Mazziotta JC and Phelps ME: Metabolic evidence of lateralized cerebral function demonstrated by positron emission tomography in patients with neuropsychiatric disorders and normal individuals. In: The Dual Brain. DF Benson and E Zaidel (eds), New York, Guilford Press, 1985, pp 181-192.

McDermott JR, Smith AI, Iqbal K and Wisniewski HM: Aluminum and Alzheimer's disease. Lancet 2: 710-711, 1977.

McDermott JR, Smith IA, Iqbal K and Wisniewski HM: Brain aluminum in aging and Alzheimer disease. Neurology 29: 809-814, 1979.

McGeer PL, McGeer EG and Suzuki JS: Aging and extrapyramidal function. Arch. Neurol. 34: 33-35, 1977.

McGeer PL, McGeer EG, Suzuki J, Dolman CE and Nagai T: Aging, Alzheimer's disease, and the cholinergic system of the basal forebrain. Neurology 34: 741-745, 1984.

McKhann G, Drachman D, Folstein M, Katzman R, Price D and Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34: 939-944, 1984.

Meier MJ and Martin WE: Intellectual changes associated with levodopa therapy. J. A. M. A. 213: 465-466, 1970.

Merz PA, Rohwer RG, Kascsak R, Wisniewski HM, Somarville RA, Gibbs CJ Jr and Gajdusek DC: Infection-specific particle from the unconventional slow virus diseases. Science 225: 437-440, 1984.

Merz PA, Rowher R, Somerville R, Wisniewski HM, Gibbs CJ Jr and Gajdusek DC: Scrapie associated fibrils in human Creutzfeldt-Jakob disease. J. Neuropathol. Exp. Neurol. 42: 327, 1983a.

Merz PA, Somerville RA and Wisniewski HM: Abnormal fibrils in scrapie and senile dementia of Alzheimer's type. In: Virus Non Conventionnels et Affections du Système Nerveux Central. LA Court and F Cathala (eds), Paris, Masson, 1983b, pp 259-281.

Merz PA, Somerville RA, Wisniewski HM and Iqbal K: Abnormal fibrils from scrapie-infected brain. Acta Neuropathol. (Berl.) 54: 63-74, 1981.

Merz PA, Somerville RA, Wisniewski HM, Manuelidis L and Manuelidis EE: Scrapie-associated fibrils in Creutzfeldt-Jakob disease. Nature 306: 474-476, 1983c.

Mesulam M-M, Mufson EJ, Levey AI and Wainer BH: Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. J. Comp. Neurol. 214: 170-197, 1983.

Meyer RK, McKinley MP, Bowman KA, Braunfeld MB, Barry RA and Prusiner SB: Separation and properties of cellular and scrapie prion proteins. Proc. Natl. Acad. Sci. USA, in press.

Mobley WC, Rutkowski JL, Tennekoon GI, Buchanan K and Johnston MV: Choline acetyltransferase activity in striatum of neonatal rats is increased by nerve growth factor. Science 229: 284-286, 1985.

Mobley WC, Server AC, Ishii DN, Riopelle RJ and Shooter EM: Nerve growth factor. NGF and disorders of the nervous system. N. Engl. J. Med. 297: 1211-1218, 1977.

Morrison JH, Rogers J, Scherr S, Benoit R and Bloom FE: Somatostatin immunoreactivity in neuritic plaques of Alzheimer's patients. Nature 314: 90-94, 1985.

Mortimer JA, French LR, Hutton JT and Schuman LM: Head injury as a risk factor for Alzheimer's disease. Neurology 35: 264-267, 1985.

Mortimer JA, Pirozzolo FJ, Hansch EC and Webster DD: Relationship of motor symptoms to intellectual deficits in Parkinson disease. Neurology 32: 133-137, 1982.

Moskowitz LB, Hensley GT, Chan JC, Gregorios J and Conley FK: The neuropathology of acquired immune deficiency syndrome. Arch. Pathol. Lab. Med. 108: 867-872, 1984.

Mountjoy CQ, Roth M, Evans NJR and Evans HM: Cortical neuronal counts in normal elderly controls and demented patients. Neurobiol. Aging 4: 1-11, 1983.

Mountjoy CQ, Tomlinson BE and Gibson RH: Amyloid and senile plaques and cerebral blood vessels. A semi-quantitative investigation of a possible relationship. J. Neurol. Sci. 57: 89-103, 1982.

Nakano I and Hirano A: Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease. Ann. Neurol. 15: 415-418, 1984.

Narayan O and Cork LC: Lentiviral diseases of sheep and goats: chronic pneumonia leukoencephalomyelitis and arthritis. Rev. Infect. Dis. 7: 89-98, 1985.

Narayan O, Griffin DE and Clements JE: Virus mutation during "slow infection": temporal development and characterization of mutants of visna virus recovered from sheep. J. Gen. Virol. 41: 343-352, 1978.

Narayan O, Griffin DE and Silverstein AM: Slow virus infection: replication and mechanisms of persistence of visna virus in sheep. J. Infect. Dis. 135: 800-806, 1977.

Narayan O, Sheffer D, Clements J and Tennekoon G: Restricted replication of lentiviruses. Visna viruses induce a unique interferon during interaction between lymphocytes and infected macrophages. J. Exp. Med., in press.

Narayan O, Silverstein AM, Price D and Johnson RT: Visna virus infection of American lambs. Science 183: 1202-1203, 1974.

Nathanson N, Martin JR, Georgsson G, Palsson PA, Lutley RE and Petursson G: The effect of post-infection immunization on the severity of experimental visna. J. Comp. Pathol. 91: 185-191, 1981.

Nathanson N, Panitch H, Palsson PA, Petursson G and Georgsson G: Pathogenesis of visna. II. Effect of immunosuppression upon early central nervous system lesions. Lab. Invest. 35: 444-451, 1976.

Nauta WJH and Feirtag M: The organization of the brain. Sci. Am. 241: 88-111, 1979.

Navia BA, Cho E-S, Petito CK and Price RW: The AIDS dementia complex. II. Neuropathology. Ann. Neurol., in press a.

Navia BA, Jordan BD and Price RW: The AIDS dementia complex. I. Clinical features. Ann. Neurol., in press b.

Nee LE, Polinsky RJ, Eldridge R, Weingartner H, Smallberg S and Ebert M: A family with histologically confirmed Alzheimer's disease. Arch. Neurol. 40: 203-208, 1983.

Nestler EJ, Walaas SI and Greengard P: Neuronal phosphoproteins: physiological and clinical implications. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 280-296.

Nielsen SL, Petito CK, Urmacher CD and Posner JB: Subacute encephalitis in acquired immune deficiency syndrome: a postmortem study. Am. J. Clin. Pathol. 82: 678-682, 1984.

Nishizuka Y: Turnover of inositol phospholipids and signal transduction. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 297-308.

Norman C: Virus scare halts hormone research. Science 228: 1176-1177, 1985.

Oesch B, Westaway D, Wälchli M, McKinley MP, Kent SBH, Abersold R, Barry RA, Tempst P, Teplow DB, Hood LE, Prusiner SB and Weissmann C: A cellular gene encodes scrapie PrP 27-30 protein. Cell 40: 735-746, 1985.

Ojika K and Appel SH: Neurotrophic factors and Alzheimer's disease. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 285-295, 1983.

Palacios JM and Kuhar MJ: Neurotensin receptors are located on dopamine-containing neurones in rat midbrain. Nature 294: 587-589, 1981

Parkinson J: An essay on the shaking palsy. London, Sherwood, Neely & Jones, 1817. Reprinted in: James Parkinson (1755-1824), A Bicentenary Volume of

Papers Dealing with Parkinson's disease. Critchley M, McMenemey WH Walshe FMR and Greenfield JG (eds), London, Macmillan, 1955.

Parsons B and Rainbow TC: High-affinity binding sites for [^{3}H]MPTP may correspond to monamine oxidase. Eur. J. Pharmacol. 102: 375-377, 1984.

Pearson RCA, Esiri MM, Hiorns RW, Wilcock GK and Powell TPS: Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. Proc. Natl. Acad. Sci. USA 82: 4531-4534, 1985.

Penney JB Jr and Young AB: Speculations on the functional anatomy of basal ganglia disorders. Annu. Rev. Neurosci. 6: 73-94, 1983.

Perl DP and Brody AR: Alzheimer's disease: x-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science 208: 297-299, 1980.

Perlmutter JS and Raichle ME: Regional blood flow in hemiparkinsonism. Neurology 35: 1127-1134, 1985.

Perry EK and Perry RH: New insights into the nature of senile (Alzheimer-type) plaques. Trends Neurosci. 8: 301-303, 1985.

Perry EK, Perry RH, Candy JM, Fairbairn AF, Blessed G, Dick DJ and Tomlinson BE: Cortical serotonin-S_2 receptor binding abnormalities in patients with Alzheimer's disease: comparisons with Parkinson's disease. Neurosci. Lett. 51: 353-357, 1984.

Perry EK, Perry RH, Tomlinson BE, Blessed G and Gibson PH: Coenzyme A-acetylating enzymes in Alzheimer's disease: possible cholinergic "compartment" of pyruvate dehydrogenase. Neurosci. Lett. 18: 105-110, 1980.

Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH and Perry RH: Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br. Med. J. 2: 1457-1459, 1978.

Perry EK, Tomlinson BE, Blessed G, Perry RH, Cross AJ and Crow TJ: Neuropathological and biochemical observations on the noradrenergic system in Alzheimer's disease. J. Neurol. Sci. 51: 279-287, 1981.

Perry G, Rizzuto N, Autilio-Gambetti L and Gambetti P: Paired helical filaments from Alzheimer disease patients contain cytoskeletal components. Proc. Natl. Acad. Sci. USA 82: 3916-3920, 1985.

Perry RH, Tomlinson BE, Candy JM, Blessed G, Foster JF, Bloxham CA and Perry ER: Cortical cholinergic deficit in mentally impaired parkinsonian patients. Lancet 2: 789-790, 1983.

Peters A, Palay SL and Webster HdeF: The Fine Structure of the Nervous System: The Neurons and Supporting Cells. Philadelphia, W.B. Saunders, 1976.

Peterson C, Gibson GE and Blass JP: Alterations of calcium transport in cultured skin fibroblasts from Alzheimer's patients. Submitted for publication.

Pétursson G, Nathanson N, Georgsson G, Panitch H and Pálsson PA: Pathogenesis of visna. I. Sequential virologic, serologic, and pathologic studies. Lab. Invest. 35: 402-412, 1976.

Popovic M, Sarngadharan MG, Read E and Gallo RC: Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 224: 497-500, 1984.

Poskanzer DC and Schwab RS: Cohort analysis of Parkinson's syndrome. Evidence for a single etiology related to subclinical infection about 1920. J. Chronic Dis. 16: 961-973, 1963.

Powers JM, Schlaepfer WW, Willingham MC and Hall BJ: An immunoperoxidase study of senile cerebral amyloidosis with pathogenetic considerations. J. Neuropathol. Exp. Neurol. 40: 592-612, 1981.

Powers RE, Struble RG, Casanova MF, O'Connor DT, Kitt CA and Price DL: Structural abnormalities of noradrenergic systems in Alzheimer's disease. Neuroscience, in press.

Price DL and Griffin JW: Neurons and ensheathing cells as targets of disease processes. In: Experimental and Clinical Neurotoxicology. PS Spencer and HH Schaumburg (eds), Baltimore, Williams & Wilkins, 1980, pp 2-23.

Price DL and Griffin JW: Structural substrate of protein synthesis and transport in spinal motor neurons. In: Amyotrophic Lateral Sclerosis: Recent Research Trends. J Andrews and R Johnson (eds), New York, Academic Press, 1976, pp 1-32.

Price DL, Cork LC, Struble RG, Kitt CA, Price DL Jr, Lehmann J and Hedreen JC: Neuropathological, neurochemical, and behavioral studies of the aging nonhuman primate. In: Behavior and Pathology of Aging in Rhesus Monkeys, Monographs in Primatology, Vol. 8. RT Davis and CW Leathers (eds), New York, Alan R. Liss, 1985a, pp 113-135.

Price DL, Griffin JW, Hoffman PN, Cork LC and Spencer PS: The response of motor neurons to injury and disease. In: Peripheral Neuropathy, Vol. I. PJ Dyck, PK Thomas, EH Lambert and R Bunge (eds), Philadelphia, W.B. Saunders, 1984, pp 732-759.

Price DL, Whitehouse PJ, Struble RG, Coyle JT, Clark AW, DeLong MR, Cork LC and Hedreen JC: Alzheimer's disease and Down's syndrome. Ann. N. Y. Acad. Sci. 396: 145-164, 1982.

Price DL, Struble RG, Altschuler RJ, Casanova MF, Cork LC and Murphy DB: Aggregation of tubulin in neurons in Alzheimer's disease. J. Neuropathol. Exp. Neurol. 44: 366, 1985b.

Price DL, Whitehouse PJ and Struble RG: Alzheimer's disease. Annu. Rev. Med. 36: 349-356, 1985c.

Price DL, Whitehouse PJ and Struble RG: Cellular pathology in Alzheimer's and Parkinson's diseases. Trends Neurosci. 9: 29-33, 1986.

Price DL, Whitehouse PJ, Struble RG, Price DL Jr, Cork LC, Hedreen JC and Kitt CA: Basal forebrain cholinergic neurons and neuritic plaques in primate brain.

Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 65-77, 1983.

Price DL: New perspectives on Alzheimer's disease. Annu. Rev. Neurosci. 9: 489-512, 1986.

Price RW, Navia BA and Cho E-S: AIDS encephalopathy. Neurol. Clin., in press b.

Probst A, Basler V, Bron B and Ulrich J: Neuritic plaques in senile dementia of Alzheimer type: a Golgi analysis in the hippocampal region. Brain Res. 268: 249-254, 1983.

Probst A, Ulrich J and Heitz PhU: Senile dementia of Alzheimer type: astroglial reaction to extracellular neurofibrillary tangles in the hippocampus. Acta Neuropathol. (Berl.) 57: 75-79, 1982.

Prusiner SB, Barry RA, McKinley MP, Bellinger CG, Meyer RK, DeArmond SJ and Kingsbury DT: Scrapie and Creutzfeldt-Jakob disease prions. Microbiol. Sci. 2: 33-39, 1985.

Prusiner SB, Groth DF, Bolton DC, Kent SB and Hood LE: Purification and structural studies of a major scrapie prion protein. Cell 38: 127-134, 1984.

Prusiner SB, McKinley MP, Bowman KA, Bolton DC, Bendheim PE, Groth DF and Glenner GG: Scrapie prions aggregate to form amyloid-like birefringent rods. Cell 35: 349-358, 1983.

Prusiner SB: Prions. Sci. Am. 251: 50-59, 1984.

Quinn NP, Rossor MJ and Marsden CD: Dementia and Parkinson's disease -- pathological and neurochemical considerations. Br. Med. Bull., in press.

Rajput AH, Offord KP, Beard CM and Kurland LT: Epidemiology of parkinsonism: incidence, classification, and mortality. Ann. Neurol. 16: 278-282, 1984.

Rasool CG and Selkoe DJ: Alzheimer's disease: exposure of neurofilament immunoreactivity in SDS-insoluble paired helical filaments. Brain Res. 322: 194-198, 1984.

Rasool CG, Abraham C, Anderton BH, Haugh M, Kahn J and Selkoe DJ: Alzheimer's disease: immunoreactivity of neurofibrillary tangles with anti-neurofilament and anti-paired helical filament antibodies. Brain Res. 310: 249-260, 1984.

Redmond DE Jr, Roth RH and Sladek JR: MPTP produces classic parkinsonian syndrome in African green monkeys. Soc. Neurosci. Abstr. 11: 166, 1985.

Reichardt LF: Immunological approaches to the nervous system. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 89-100.

Report of the Secretary's Task Force on Alzheimer's Disease. Washington, D.C., U.S. Department of Health and Human Services, 1984.

Reynolds GP, Arnold L, Rossor MN, Iversen LL, Mountjoy CQ and Roth M: Reduced binding of [^{3}H]ketanserine to cortical 5-HT$_2$ receptors in senile dementia of the Alzheimer type. Neurosci. Lett. 44: 47-51, 1984.

Riederer P and Wuketich St: Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis. J. Neural. Transm. 38: 277-301, 1976.

Roberts GW, Crow TJ and Polak JM: Location of neuronal tangles in somatostatin neurones in Alzheimer's disease. Nature 314: 92-94, 1985.

Roos R, Gajdusek DC and Gibbs CJ Jr: The clinical characteristics of transmissible Creutzfeldt-Jakob disease. Brain 96: 1-20, 1973.

Rossor MN, Emson PC, Mountjoy CQ, Roth M and Iversen LL: Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of Alzheimer type. Neurosci. Lett. 20: 373-377, 1980.

Rossor MN, Svendsen C, Hunt SP, Mountjoy CQ, Roth M and Iversen LL: The substantia innominata in Alzheimer's disease: an histochemical and biochemical study of cholinergic marker enzymes. Neurosci. Lett. 28: 217-222, 1982.

Roth M: Diagnosis of senile and related forms of dementia. In: Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol. 7). R Katzman, RD Terry and KL Bick (eds), New York, Raven Press, 1978, pp 71-85.

Ruberg M, Ploska A, Javoy-Agid F and Agid Y: Muscarinic binding and choline acetyltransferase activity in parkinsonian subjects with reference to dementia. Brain Res. 232: 129-139, 1982.

Sajdel-Sulkowska EM and Marotta CA: Alzheimer's disease brain: alterations in RNA levels and in a ribonuclease-inhibitor complex. Science 225: 947-949, 1984.

Sajdel-Sulkowska EM, Coughlin FJ, Staton DM and Marotta CA: In vitro protein synthesis by messenger RNA from the Alzheimer's disease brain. Biological Aspects of Alzheimer's Disease. Banbury Rep. 15: 193-200, 1983.

Sanberg PR and Coyle JT: Scientific approaches to Huntington's disease. CRC Crit. Rev. Clin. Neurobiol. 1: 1-44, 1984.

Saper CB, German DC and White CL III: Neuronal pathology in the nucleus basalis and associated cell groups in senile dementia of the Alzheimer's type: possible role in cell loss. Neurology 35: 1089-1095, 1985.

Scatton B, Javoy-Agid F, Rouquier L, Dubois B and Agid Y: Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res. 275: 321-328, 1983.

Schnapp BJ, Vale RD, Sheetz MP and Reese TS: Single microtubules from squid axoplasm support bidirectional movement of organelles. Cell 40: 455-462, 1985.

Schneider E, Fischer PA, Becker H, Hacker H, Pencz A and Jacobi P: Relationship between artheriosclerosis and cerebral atrophy in Parkinson's disease. J. Neurol. 217: 11-16, 1977.

Schramm M and Selinger Z: Message transmission: receptor controlled adenylate cyclase system. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 266-279.

Seiler M and Schwab ME: Specific retrograde transport of nerve growth factor (NGF) from neocortex to nucleus basalis in the rat. Brain Res. 300: 33-39, 1984.

Selby G: Parkinson's disease. In: Diseases of the Basal Ganglia, Handbook of Clinical Neurology, Vol. 6. PJ Vinken and GW Bruyn (eds), Amsterdam, North-Holland Publishing Co., 1968, pp 173-211.

Selkoe DJ and Abraham CR: Isolation of paired helical filaments and amyloid fibers from human brain. Submitted for publication.

Selkoe DJ, Abraham C and Ihara Y: Brain transglutaminase: in vitro crosslinking of human neurofilament proteins into insoluble polymers. Proc. Natl. Acad. Sci. USA 79: 6070-6074, 1982.

Selkoe DJ, Liem RKH, Yen S-H and Shelanski ML: Biochemical and immunological characterization of neurofilaments in experimental neurofibrillary degeneration induced by aluminum. Brain Res. 163: 235-252, 1979.

Selkoe DJ: Structural proteins in Alzheimer's disease. In: Proceedings of the IVth World Congress of Biological Psychiatry. New York, Elsevier, in press.

Seltzer B and Sherwin I: A comparison of clinical features in early- and late-onset primary degenerative dementia. One entity or two? Arch. Neurol. 40: 143-146, 1983.

Shaw GM, Harper ME, Hahn BH, Epstein LG, Gajdusek DC, Price RW, Navia BA, Petito CK, O'Hara CJ, Groopman JE, Cho E-S, Oleske JM, Wong-Staal F and Gallo RC: HTLV-III infection in brains of children and adults with AIDS encephalopathy. Science 227: 177-181, 1985.

Shefer VF: Absolute numbers of neurons and thickness of the cerebral cortex during aging, senile and vascular dementia, and Pick's and Alzheimer's diseases. Neurosci. Behav. Physiol. 6: 319-324, 1973.

Sheffield WD, Narayan O, Strandberg JD and Adams RJ: Visna-Maedi like disease associated with an ovine retrovirus infection in a corriedale sheep. Vet. Pathol. 17: 544-552, 1980.

Shoulson I: Care of patients and families with Huntington's disease. In: Movement Disorders, Neurology, Vol. 2. CD Marsden and S Fahn (eds), London, Butterworth Scientific, 1982, pp 277-290.

Shoulson I: Huntington's disease: overview of experimental therapeutics. In: Huntington's Disease, Advances in Neurology, Vol. 23. TN Chase, NX Wexler and A Barbeau (eds), New York, Raven Press, 1979, pp 751-757.

Sigurdsson B and Pálsson PA: Visna of sheep. A slow, demyelinating infection. Br. J. Exp. Pathol. 39: 519-528, 1958.

Sigurdsson B, Pálsson PA and Van Bogaert L: Pathology of visna. Transmissible demyelinating disease in sheep in Iceland. Acta Neuropathol. (Berl.) 1: 343-362, 1962.

Sims NR, Bowen DM, Allen SJ, Smith CCT, Neary D, Thomas DJ and Davison AN: Presynaptic cholinergic dysfunction in patients with dementia. J. Neurochem. 40: 503-509, 1983.

Sjogren T, Sjogren H and Lindgren AGH: Morbus Alzheimer and morbus Pick. A genetic, clinical and patho-anatomical study. Acta Psychiatr. Neurol. Scand. (Suppl.) 82: 1-152, 1952.

Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE and Posner JB: Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann. Neurol. 14: 403-418, 1983.

Snyder SH and D'Amato RJ: MPTP: a neurotoxin relevant to the pathophysiology of Parkinson's disease. The 1985 George C. Cotzias Lecture. Neurology 36: 250-258, 1986.

Snyder SH: Drug and neurotransmitter receptors in the brain. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985a, pp 332-352.

Snyder SH: Neurosciences: an integrative discipline. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985b, pp 1-9.

Sotelo J, Gibbs CJ Jr and Gajdusek DC: Autoantibodies against axonal neurofilaments in patients with kuru and Creutzfeldt-Jakob disease. Science 210: 190-193, 1980.

Stern Y and Langston JW: Intellectual changes in patients with MPTP-induced parkinsonism. Neurology 35: 1506-1509, 1985.

Sternberger NH, Sternberger LA and Ulrich J: Aberrant neurofilament phosphorylation in Alzheimer disease. Proc. Natl. Acad. Sci. USA 82: 4274-4276, 1985.

Stevens CF: Biophysical studies of ion channels. In: Neuroscience. PH Abelson, E Butz and SH Snyder (eds), Washington, D.C., The American Association for the Advancement of Science, 1985, pp 239-247.

Stevens CF: The neuron. Sci. Am. 241: 54-65, 1979.

Stowell RE, Smith EK, España C and Nelson VG: Outbreak of malignant lymphoma in rhesus monkeys. Lab. Invest. 25: 476-479, 1971.

Stowring L, Haase AT, Petursson G, Georgsson G, Palsson P, Lutley R, Roos R and Szuchet S: Detection of visna virus antigens and RNA in glial cells in foci of demyelination. Virology 141: 311-318, 1985.

Struble RG, Cork LC, Whitehouse PJ and Price DL: Cholinergic innervation in neuritic plaques. Science 216: 413-415, 1982.

Struble RG, Hedreen JC, Cork LC and Price DL: Acetylcholinesterase activity in senile plaques of aged macaques. Neurobiol. Aging 5: 191-198, 1984a.

Struble RG, Kitt CA, Walker LC, Cork LC and Price DL: Somatostatinergic neurites in senile plaques of aged non-human primates. Brain Res. 324: 394-396, 1984b.

Struble RG, Lehmann J, Mitchell SJ, Cork LC, Coyle JT, Price DL, DeLong MR and Antuono PG: Cortical cholinergic innervation: distribution and source in monkeys. In: Dynamics of Cholinergic Function. I Hanin (ed), New York, Plenum Press, in press a.

Struble RG, Lehmann J, Mitchell SJ, McKinney M, Price DL, Coyle JT and DeLong MR: Basal forebrain neurons provide major cholinergic innervation of primate neocortex. Neurosci. Lett., in press b.

Struble RG, Powers RE, Casanova MF, Kitt CA, O'Connor DT and Price DL: Multiple transmitter-specific markers in senile plaques in Alzheimer's disease. J. Neuropathol. Exp. Neurol. 44: 325, 1985a.

Struble RG, Powers RE, Casanova MF, Kitt CA, O'Connor DT and Price DL: Multiple transmitter-specific markers in senile plaques in Alzheimer's disease. Soc. Neurosci. Abstr. 11: 953, 1985b.

Struble RG, Price DL Jr, Cork LC and Price DL: Senile plaques in cortex of aged normal monkeys. Brain Res. 361: 267-275, 1985c.

Svennilson E, Torvik A, Loew R and Leksell L: Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases. Acta Psychiatr. Neurol. Scand. 35: 358-377, 1960.

Terry RD and Katzman R: Senile dementia of the Alzheimer type. Ann. Neurol. 14: 497-506, 1983.

Terry RD: Neurofibrillary tangles and cytoskeletal proteins. J. Neuropathol. Exp. Neurol. 40: 317, 1981.

Thoenen H and Barde YA: Physiology of nerve growth factor. Physiol. Rev. 60: 1284-1335, 1980.

Tomlinson BE and Kitchener D: Granulovacuolar degeneration of hippocampal pyramidal cells. J. Pathol. 106: 165-185, 1972.

Tomlinson BE, Blessed G and Roth M: Observations on the brains of demented old people. J. Neurol. Sci. 11: 205-242, 1970.

Tomlinson BE, Blessed G and Roth M: Observations on the brains of non-demented old people. J. Neurol. Sci. 7: 331-356, 1968.

Tomlinson BE, Irving D and Blessed G: Cell loss in the locus coeruleus in senile dementia of Alzheimer type. J. Neurol. Sci. 49: 419-428, 1981.

Troncoso JC, Hoffman PN, Griffin JW, Hess-Kozlow KM and Price DL: Aluminum intoxication: a disorder of neurofilament transport in motor neurons. Brain Res. 342: 172-175, 1985.

Troncoso JC, Price DL, Griffin JW and Parhad IM: Neurofibrillary axonal pathology in aluminum intoxication. Ann. Neurol. 12: 278-283, 1982.

Troncoso JC, Sternberger NH, Sternberger LA, Hoffman PN and Price DL: Immunocytochemical studies of neurofilament antigens in the neurofibrillary pathology induced by aluminum. Brain Res. 364: 295-300, 1986.

Truman JW and Schwartz LM: Insect systems for the study of programmed neuronal death. Neurosci. Comment. 1: 73-83, 1982.

Uhl GR, Hedreen JC and Price DL: Parkinson's disease: loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology 35: 1215-1218, 1985.

Uhl GR, Whitehouse PJ, Price DL, Tourtellotte WW and Kuhar MJ: Parkinson's disease: depletion of substantia nigra neurotensin receptors. Brain Res. 308: 186-190, 1984.

Vale RD, Reese TS and Sheetz MP: Identification of a novel force-generating protein, kinesin, involved in microtubule-based motility. Cell 42: 39-50, 1985a.

Vale RD, Schnapp BJ, Reese TS and Sheetz MP: Movement of organelles along filaments dissociated from the axoplasm of the squid giant axon. Cell 40: 449-454, 1985b.

Vale RD, Schnapp BJ, Reese TS and Sheetz MP: Organelle, bead, and microtubule translocations promoted by soluble factors from the squid giant axon. Cell 40: 559-569, 1985c.

Walker LC, Kitt CA, Struble RG, Schmechel DE, Oertel WH, Cork LC and Price DL: Glutamic acid decarboxylase-like immunoreactivity in senile plaques. Neurosci. Lett. 59: 165-169, 1985.

Wells CE: Dementia, Edition 2, Contemporary Neurology Series. Philadelphia, F.A. Davis, 1977.

Wexler NS, Conneally PM, Housman D and Gusella JF: A DNA polymorphism for Huntington's disease marks the future. Arch. Neurol. 42: 20-24, 1985.

Whitehouse PJ, Hedreen JC, White CL III and Price DL: Basal forebrain neurons in the dementia of Parkinson disease. Ann. Neurol. 13: 243-248, 1983.

Whitehouse PJ, Martino AM, Antuono PG, Lowenstein PR, Coyle JT, Price DL and Kellar KJ: Nicotinic acetylcholine binding in Alzheimer's disease. Brain Res., in press a.

Whitehouse PJ, Martino AM, Marcus K, Price DL and Kellar KJ: Alterations in [^{3}H] acetylcholine binding in cortex in Alzheimer's disease. Brain Res., in press b.

Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT and DeLong MR: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science 215: 1237-1239, 1982.

Whitehouse PJ, Trifiletti RR, Jones BE, Folstein S, Price DL, Snyder SH and Kuhar MJ: Neurotransmitter receptor alterations in Huntington's disease: autoradiographic and homogenate studies with special reference to benzodiazepine receptor complexes. Ann. Neurol. 18: 202-210, 1985.

Whitehouse PJ: Receptor autoradiography: applications in neuropathology. Trends Neurosci. 8: 434-437, 1985.

Wilcock GK and Esiri MM: Plaques, tangles and dementia. A quantitative study. J. Neurol. Sci. 56: 343-356, 1982.

Wischik CM, Crowther RA, Stewart M and Roth M: Subunit structure of paired helical filaments in Alzheimer's disease. J. Cell Biol. 100: 1905-1912, 1985.

Wisniewski HM and Terry RD: Reexamination of the pathogenesis of the senile plaque. In: Progress in Neuropathology, Vol. II. HM Zimmerman (ed), New York, Grune & Stratton, 1973, pp 1-26.

Wisniewski HM, Bruce ME and Fraser H: Infectious etiology of neuritic (senile) plaques in mice. Science 190: 1108-1110, 1975.

Wisniewski KE, Dalton AJ, Crapper McLachlan DR, Wen GY and Wisniewski HM: Alzheimer's disease in Down's syndrome: clinicopathologic studies. Neurology 35: 957-961, 1985.

Wisniewski HM, Ghetti B and Terry RD: Neuritic (senile) plaques and filamentous changes in aged rhesus monkeys. J. Neuropathol. Exp. Neurol. 32: 566-584, 1973.

Wisniewski HM, Merz PA and Iqbal K: Ultrastructure of paired helical filaments of Alzheimer's neurofibrillary tangle. J. Neuropathol. Exp. Neurol. 43: 643-656, 1984.

Wisniewski HM, Moretz RC and Lossinsky AS: Evidence for induction of localized amyloid deposits and neuritic plaques by an infectious agent. Ann. Neurol. 10: 517-522, 1981.

Wisniewski HM, Narang HK and Terry RD: Neurofibrillary tangles of paired helical filaments. J. Neurol. Sci. 27: 173-181, 1976.

Wisniewski K, Howe J, Williams DG and Wisniewski HM: Precocious aging and dementia in patients with Down's syndrome. Biol. Psychiatry 13: 619-627, 1978.

Yamamoto T and Hirano A: Nucleus raphe dorsalis in Alzheimer's disease: neurofibrillary tangles and loss of large neurons. Ann. Neurol. 17: 573-577, 1985.

Yates CM, Gordon A and Wilson H: Neurofibrillary degeneration induced in the rabbit by aluminum chloride: aluminum neurofibrillary tangles. Neuropathol. Appl. Neurobiol. 2: 131-144, 1976.

Yates CM, Simpson J, Gordon A, Maloney AFJ, Allison Y, Ritchie IM and Urquhart A: Catecholamines and cholinergic enzymes in pre-senile and senile Alzheimer-type dementia and Down's syndrome. Brain Res. 280: 119-126, 1983.

Yen S-H, Crowe A and Dickson DW: Monoclonal antibodies to Alzheimer neurofibrillary tangles. 1. Identification of polypeptides. Am. J. Pathol. 120: 282-291, 1985.

Zetusky WJ, Jankovic J and Pirozzolo FJ: The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 35: 522-526, 1985.

FIGURES

Figure 1

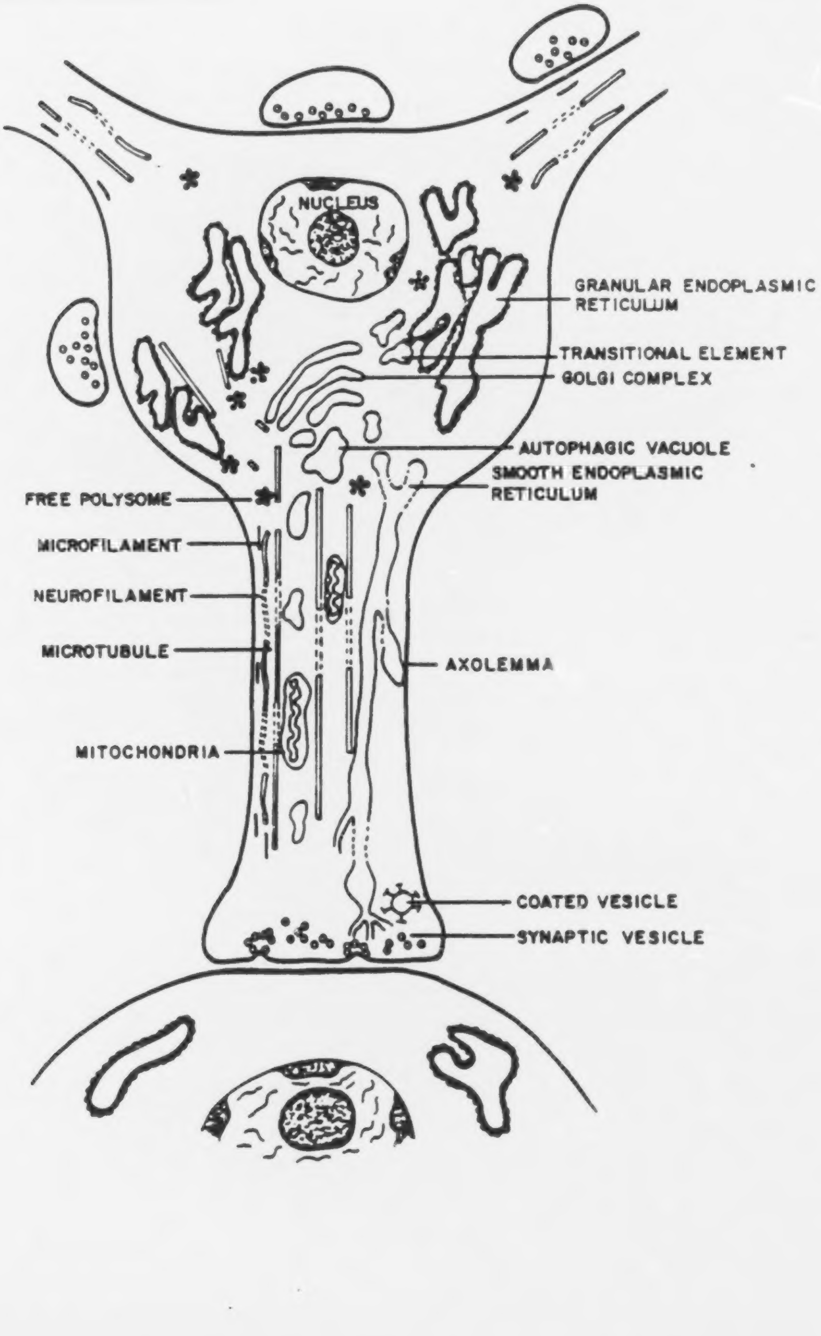

NUCLEUS
GRANULAR ENDOPLASMIC RETICULUM
TRANSITIONAL ELEMENT
GOLGI COMPLEX
AUTOPHAGIC VACUOLE
SMOOTH ENDOPLASMIC RETICULUM
FREE POLYSOME
MICROFILAMENT
NEUROFILAMENT
MICROTUBULE
AXOLEMMA
MITOCHONDRIA
COATED VESICLE
SYNAPTIC VESICLE

Figure 1: Schematic drawing of two neurons (principal nerve cell and target), illustrating the functional and structural elements of a nerve cell, with emphasis on axonal elements important in protein synthesis, transport, and synaptic transmission [Price and Griffin, 1976].

The cell body contains a nucleus, a nucleolus, granular endoplasmic reticulum, transitional elements, Golgi complexes, and mitochondria.

DNA is transcribed in the nucleus, and RNA and mRNA are transported to cytoplasm, where they play essential roles in the translation of proteins.

Slowly transported proteins (left side) (e.g., actin, tubulin, and the neurofilament triplet proteins) are synthesized on free polysomes and self assembled into microfilaments, neurofilaments, and microtubules, respectively. These organelles are the major components of the neuronal cytoskeleton.

Rapidly transported, membrane-associated proteins (right side) are synthesized by ribosomes of the granular endoplasmic reticulum and, subsequently, become associated with the smooth endoplasmic reticulum. Some polypeptides are transported from the granular endoplasmic reticulum via transitional elements to the Golgi apparatus. These rapidly transported, membrane-associated proteins and glycoproteins are delivered by kinesin-mediated interactions with microtubules to the axolemma and to nerve terminals. They serve to renew the axolemma and provide membranes for synaptic terminals. The retrograde transport system carries both endogenous and exogenous elements from distal axons and nerve terminals toward the cell body.

Exogenous proteins can bind to receptors on the surface of nerve terminals or can be taken up by fluid-phase endocytosis; subsequently, they are carried retrograde to the cell body.

The synaptic terminal is rich in vesicles that contain neurotransmitter molecules. When an action potential depolarizes the terminal, vesicles move to and fuse with active zones, and transmitter is released by exocytosis. The transmitter diffuses across the synaptic cleft and binds to receptors expressed on the surface of the target cell. This binding of transmitter to receptor causes conduction and/or resistence changes in the target cell. Similar synaptic inputs, depicted on the cell body and proximal dendrites, influence the behavior of the principal neuron.

Figure 2

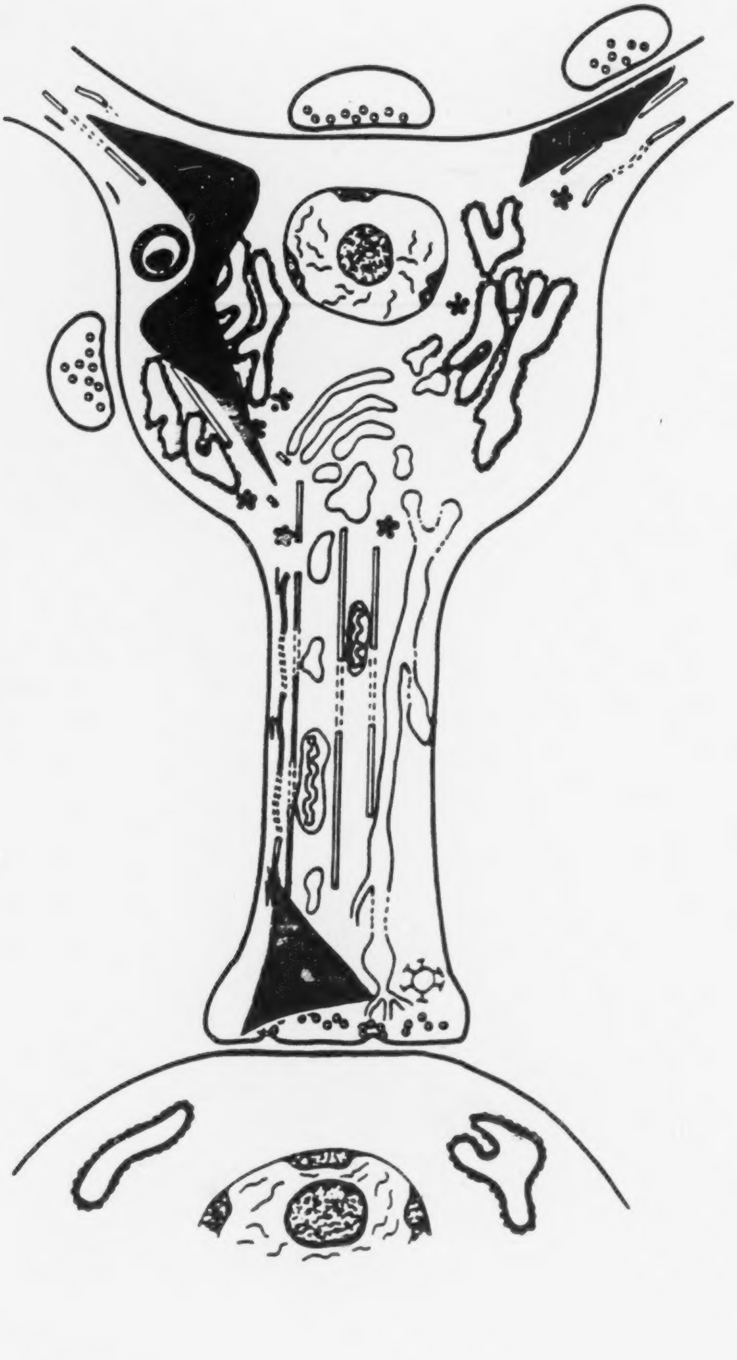


Figure 2: This schematic drawing depicts a neuron showing several types of pathology occurring in AD.

Note the nucleus, normal organelles within the cell body, proximal dendrites, axon, and nerve terminal. A target neuron and a cerebral capillary (lower right-hand corner) are also depicted. Conventional symbols (see Figure 1) are used to show normal organelles, including rough endoplasmic reticulum, free polysomes, Golgi apparatus, microtubules, neurofilaments, microfilaments, mitochondria, endoplasmic reticulum, and synaptic vesicles. The neuron receives three synaptic inputs and synapses upon a target cell.

Four types of neuronal pathology and two forms of amyloid are illustrated. NFT are indicated by the lightning bolt-shaped structure on the left side of the perikarya. Adjacent to NFT is a GVD. Within a dendrite (upper right) is a rhomboid-shaped Hirano body. The distal axon/nerve terminal contains accumulations of filaments (triangle). In proximity to the nerve terminal and target cell are amyloid deposits (linear fibrils). This amyloid is associated with a senile plaque. In addition, amyloid is deposited in proximity to the blood vessel.

TABLES

I. DISORDERS CAUSING DEMENTIA (a partial list)

Degenerative Diseases of the CNS

- Alzheimer's disease
- Parkinson's disease
- Parkinson-dementia complex of Guam
- Pick's disease
- Progressive supranuclear palsy

Genetic Disorders

- Huntington's disease
- Alzheimer's disease, familial type
- Wilson's disease
- Lipid storage diseases

Nonneuronal Metabolic Disorders

- Parathyroid disease
- Myxedema
- Liver disease
- Metachromatic leukodystrophy

Deficiency Diseases

- Wernicke-Korsakoff syndrome
- Vitamin B12 deficiency

Intoxications

- Dialysis dementia
- Carbon monoxide exposure
- Drug abuse

Cerebrovascular Diseases

- Multi-infarct dementia
- Vasculitis

Hypoxia

(continued on next page)

Infections

- Creutzfeldt-Jakob disease
- Acquired immune deficiency syndrome
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis
- Brain abscess
- Meningitis
- Encephalitis

Brain Tumors

Normal Pressure Hydrocephalus

II. NEUROBIOLOGICAL APPROACHES

Biological Question	Techniques	Representative Examples
Roles of genes or genetic elements (e.g., viruses)	Recombinant DNA techniques	Localization of HD gene to chromosome 4; demonstration of retrovirus in brain tissue of AIDS patients
Changes in RNAs	Measurements of RNAs (Northern blots and *in situ* hybridization, etc.) and enzymes acting on RNAs	Reduction of RNA levels in AD
Changes in proteins	Incorporation studies of amino acids; SDS gels; Western blots; immunocytochemistry	Reduction of protein synthesis in AD; aberrant phosphorylation of 200-kd neurofilament protein associated with NFT in AD and with Lewy bodies in PD
Character of proteins in abnormal organelles	Purification of constituents; analysis of proteins and other components; protein sequencing; immunocytochemistry; freeze-fracture/deep-etch	Decoration of PHF with antiMAP2 and antineurofilament antibodies; tubulin in granolovacuolar degeneration; actin in Hirano bodies; amyloid protein in congophilic angiopathy
Axonal transport of proteins	Radiolabeling, followed by gel fluorography	Impaired transport of neurofilament proteins in neurofibrillary pathology of aluminum poliomyelopathy
Altered transmitters and enzymes	Neurochemical assays; radioimmunoassays	In AD, reduction of cortical ChAT, somatostatin, and CRF
Changes in receptors	Binding assays, *in vitro* autoradiography	In AD, reduction of somatostatin and M2 cortical cholinergic receptors and increased cortical CRF receptors
Changes in neuronal shape and size	Golgi stains	Abnormal dendritic arborizations in AD and HD
Structural abnormalities of specific neurons	Immunocytochemistry	In AD, localization of NFT in cholinergic and somatostatinergic neurons; noradrenergic neurites in plaques

(continued on next page)

Distribution of pathological changes in specific brain regions	Computer-assisted morphometric methods	In AD, reduction of numbers of neurons in the nucleus basalis, hippocampus, and neocortex
Roles of specific systems in behavior	Lesion studies; behavioral tests	Memory impairments following bilateral lesions of the nucleus basalis in nonhuman primates
Abnormalities in specific brain regions	Computerized tomography; magnetic resonance imaging; PET	Cerebral atrophy in AD and AIDS; infarcts in multi-infarct dementia; white matter lesions in AIDS; hypometabolism in striatum in HD and in cortex in AD
Role of infectious agents in disease	Immunological studies; transmission studies; culture of virus	Transmission of CJD to nonhuman primates; isolation of virus in AIDS
Composition of infectious agents	Methods of molecular virology	Characterization of retrovirus in AIDS as a type of lentivirus; unconventional nature of virus causing CJD
Treatment strategies	Drug trials; tissue grafts	L-dopa in PD and MPTP model; neural grafts improve functions of animals with lesions in the SNpc

III. METHODOLOGIES OF POTENTIAL VALUE USED IN STUDIES OF HUMAN DEMENTIA OR IN STUDIES OF ANIMALS SHOWING CERTAIN FEATURES RESEMBLING THOSE IN HUMAN DISEASES

Clinical Investigations

- Clinical examinations
- Neuropsychological assessments
- Epidemiological analyses of risk factors, including genetic processes
- EEG, evoked potentials
- Examinations of body fluids (including CSF) and peripheral tissues
- Computerized tomography
- Single-photon emission tomography
- Magnetic resonance imaging
- PET
- Brain biopsy

Morphological Approaches

- Light and electron microscopy
- Freeze-fracture, deep-etch techniques
- Golgi preparations
- Histochemistry and immunocytochemistry
- *In situ* hybridization
- *In vitro* receptor autoradiography
- Computer-assisted morphometry
- Techniques for tracing anatomical pathways and delineating synaptic interactions of neurons

Chemical Studies

- Enzyme assays
- Measurement of transmitter markers, including receptors
- Analysis of axonal transport of specific proteins
- Protein purification and sequencing

Physiological Analyses

- Extracellular recording
- Intracellular recording
- Patch clamp studies

Molecular Biological Strategies

- Linkage studies with recombinant DNA techniques
- Isolation and identification of genes
- Gene sequencing
- Analysis of transcriptional and translational processes

(continued on next page)

Immunological-Immunocytochemical Approaches

- Radioimmunoassays
- Western blots
- Development of immunological probes for specific antigens
- Analysis of surface markers of specific properties of cells
- Definition of functions of lymphocyte subsets
- Analysis of the effects of disease on the immune system and role of the immune system in disease

Virological Methods

- Viral culture, isolation, and characterization
- Inoculation-transmission studies
- Techniques for delineating viral cell tropisms

APPENDICES

I. RECOMMENDATIONS FOR RESEARCH ON DEMENTIA (a selected list)

Clinical Studies

- Investigate cognitive changes seen with aging and their relationship to those seen in dementia
- Investigate new concepts from cognitive psychology to clarify aspects of dementia
- Correlate clinical subtypes with laboratory studies and neuropathological-neurochemical investigations in tissues obtained postmortem

Diagnostic Advances

- Develop functional mapping methods to identify specific brain regions associated with cognition, memory, behavior, motivation, etc., and, eventually, evaluate these changes in specific diseases
- Investigate PET and magnetic resonance imaging to map changes in the brain in specific diseases
- Correlate computerized tomography, PET, and magnetic resonance images with neuropathological and neurochemical analyses of brains obtained postmortem
- Develop more accurate diagnostic measures, with emphasis on delineating markers specific for disease (e.g., PHF antigens in CSF in AD, genetic markers for HD and AD, markers for CJD, etc.)
- Develop new approaches to examine peripheral tissues, e.g., lymphocytes, skin, etc., for markers useful in diagnostic studies of some of these disorders

Neuropathology and Neurochemistry

- Study, with computer-assisted methods, specific cell populations (e.g., cholinergic and peptidergic neurons, etc.) and their constituents (e.g., mRNAs, proteins, etc.) in controls and in individuals with disease
- Study, using biochemical techniques, transmitter markers and receptors in brain tissue obtained from controls and from diseased individuals
- Characterize abnormalities in specific genes, mRNAs, and proteins in neurons in different diseases
- Determine age-associated changes in brain and the possible roles of intrinsic and extrinsic factors in these processes

- Delineate the neuropathology, neurotropism, and mechanisms of cell injury in AIDS and CJD

Etiologies

- Epidemiological studies to determine risk factors
- Study genetic factors leading directly to disease or predisposing to disease
- Study the roles of long-term exposure to environmental toxins
- Study the roles of trophic factors
- Clarify how trisomy-21 (Down's syndrome) leads to the early development of AD
- Clarify the ways in which an abnormality on chromosome 4 leads to pathology in specific cells in the striatum, and possibly cortex, in HD
- Clarify the relationships between retroviral CNS infection and dementia in the absence of significant inflammatory changes

Treatment

- Develop markers to detect and, thereby, possibly prevent genetic diseases
- Develop models for testing innovative therapies, including new pharmacological agents, trophic factors, and neural grafts
- Develop drugs and vaccines effective in treating/preventing infections caused by viruses or unconventional agents

Basic Science

- Clarify molecular mechanisms involved in processing and metabolism of neuropeptides
- Elucidate mechanisms governing transmitter storage, release, action, and metabolism
- Clarify mechanisms by which receptor-mediated signals are translated into biological events
- Study differential effects of colocalized transmitters on target cells
- Study the effects of psychopharmacological agents on neurotransmission and neuromodulation
- Characterize specific neuronal systems at risk in dementia using anatomical, physiological, and biochemical techniques

- Study the roles of these systems in normal cognitive processes and the effects of experimental lesions on animal behavior
- Study animals, combining anatomical, physiological, and pharmacological techniques with innovative behavioral paradigms to study the functions of higher brain centers important in cognition and memory
- Develop animal models of dementia
- Develop animal models to examine, using neurobiological approaches, the pathogeneses and consequences of specific molecular and cellular abnormalities
- Clone genes coding for transmitter enzymes, neuropeptides, ion channels, receptors, and components of second messenger systems, followed by studies in which this information is used to explore the roles of coded proteins in the functions of normal brain and how these proteins may be regulated in normal individuals and altered in affected individuals
- Study, using molecular biology, the regulation of expression of genes in neurons and glia
- Study gene expression mediated by hormones
- Study neurotoxins that affect the neuronal cytoskeleton or neurotransmission
- Analyze interactions of exogenous agents (e.g., viruses, toxins, etc.) on specific groups of neurons and the mechanisms leading to cell injury/death *in vivo* and *in vitro*
- Develop techniques of transplantation of tissues into the nervous system
- Develop experimental studies of regeneration and reinnervation (e.g., investigations on simple axotomy, "bridges" from source to target, and neural grafts)
- Purify, characterize, and prepare trophic factors and generate agents that can interfere with (antibodies) or bind (receptors) these trophic factors
- Study the roles of axonal transport in normal neurons and in neurons affected in neurological diseases
- Investigate the pathogeneses of infections with retroviruses or unconventional viruses, with emphasis on viral-cell tropisms and mechanisms of selective vulnerability
- Study the ways in which viral infections cause structural and functional abnormalities of target cells
- Clarify interactions of viruses, neural cells, and immune responses, particularly as occurs in persistent viral infections

- Characterize unconventional agents causing spongiform encephalopathies
- Analyze the roles of cell- and antibody-mediated immunological processes in neurological disorders
- Clarify the ways in which infectious and toxic agents cross the blood-brain barrier
- Study the roles of different types of immunological cells in the production of or protection from disease

Administration/Funding

- Support the training of young physicians and scientists to investigate dementia
- Support young investigators during the transition to independent investigators
- Encourage multidisciplinary training programs with a strong record of generating basic scientists, clinical investigators, and physician-scientists
- Support the training of clinicians and basic scientists in experimental neuropathology in a setting in which neuropathological training is complemented by excellent programs in clinical neurology and basic neuroscience
- Support an increase in the most important type of NIH research grant (i.e., the investigator-initiated R01) with emphasis on five years of continuous funding
- Support outstanding Program Project grants or Multidisciplinary Centers

II. LETTER TO CONSULTANTS

The following letter was sent to the scientists listed in Appendix III, each of whom responded with copies of pertinent reprints.

> Dear Dr. (name):
>
> I have recently been approached by the Office of Technology Assessment (a nonpartisan support agency of the Congress of the United States) to write a report discussing issues related to disorders causing dementia. The purpose of this document is to examine relationships between basic neuroscience research and investigations of different types of dementia including, but not limited to, Alzheimer's disease. I plan to review selected aspects of recent literature and indicate new directions for clinical and basic research. This document will serve as a chapter on Federal Research Policy in the field. Because of your interest in this area, I am writing to you to request recent reprints of your work as well as your comments concerning the importance of interactions between basic and clinical neuroscience as they pertain to the problem of dementia.
>
> Thank you for your assistance. I have enclosed an envelope label to make your reply more convenient.

III. LIST OF CONSULTANTS

Dr. Y. Agid
Experimental Medicine Laboratory
CHU Pitie-Salpétriére
7564, Paris, FRANCE

Albert J. Aguayo, M.D.
Clinical Neurology/Neurosciences Unit
The Montreal General Hospital
1650 Cedar
Montreal, Quebec H3G 1A4, CANADA

Marilyn S. Albert, Ph.D.
Department of Psychiatry
Massachusetts General Hospital
Bulfinch 3 (Hackett)
Fruit Street
Boston, Massachusetts 02114

Stanley H. Appel, M.D.
Department of Neurology
Baylor College of Medicine
Houston, Texas 77030

Melvyn Ball, M.D., F.R.C.P.
Departments of Pathology, Clinical Neurological Sciences, and Psychiatry
Health Sciences Centre
The University of Western Ontario
London, Ontario, N6A 5C1, CANADA

Dr. Raymond T. Bartus
Department of Central Nervous System Research
Medical Research Division
American Cyanamid Corporation
Lederle Laboratories
Pearl River, New York 10965

Dr. Frank Benson
Department of Neurology
University of California at Los Angeles School of Medicine
900 Veterans Avenue
Los Angeles, California 90024

Dr. Leonard Berg
Department of Neurology and Neurological Surgery
Washington University School of Medicine
660 Euclid Street
St. Louis, Missouri 63110

John Blass, M.D., Ph.D.
Departments of Neurology and Medicine
Cornell University Medical College, Burke Rehabilitation Center
785 Mamaroneck Avenue
White Plains, New York 10605

Dr. Garry Blessed
Newcastle General Hospital
Newcastle upon Tyne NE4 6BE, UNITED KINGDOM

Francois Boller, M.D., Ph.D.
Department of Neurology
University of Pittsburgh School of Medicine
322 Scaife Hall
Pittsburgh, Pennsylvania 15261

Dr. David Bowen
Institute of Neurology
33 Johns Mews
London WC1, UNITED KINGDOM

Dr. T. Budinger
Donner Laboratory
University of California
Berkeley, California 94705

Donald B. Calne, M.D.
Division of Neurology
Room S129, Health Sciences Center Hospital
2211 Wesbrook Mall
Vancouver, British Columbia V6T 1W5, CANADA

Dr. Arvid Carlsson
Department of Pharmacology
University of Gothenburg
Gothenburg S 400 33, SWEDEN

Paul D. Coleman, Ph.D.
Department of Anatomy
University of Rochester School of Medicine
Rochester, New York 14642

Linda C. Cork, D.V.M., Ph.D.
Neuropathology Laboratory
The Johns Hopkins University School of Medicine
509 Pathology Building
600 North Wolfe Street
Baltimore, Maryland 21205-2182

Susanne H. Corkin, Ph.D.
Department of Psychology

Massachusetts Institute of Technology, E 25-604
Cambridge, Massachusetts 02139

Carl W. Cotman, Ph.D.
Department of Psychobiology
University of California
Irvine, California 92717

Dr. Thomas Crook
Center for Studies of Mental Health of the Aging
National Institute of Mental Health
Rockville, Maryland 20857

Peter Davies, Ph.D.
Albert Einstein College of Medicine of Yeshiva University
Department of Pathology
1300 Morris Park Avenue
Bronx, New York 10461

Kenneth L. Davis, M.D.
Psychiatry Service
Bronx Veterans Administration Medical School
Departments of Psychiatry and Pharmacology
Mount Sinai School of Medicine
130 West Kingsbridge Road
Bronx, New York 10468

Piers C. Emson, Ph.D.
Neurochemical Pharmacology Unit, Department of Neurology
Medical Research Council Center
Addenbrooke's Hospital
Hills Road, Cambridge CB2 2QQ, UNITED KINGDOM

Dr. Charles J. Epstein
Department of Pediatrics, 650-M
University of California School of Medicine
San Francisco, California 94143

Dr. M. M. Esiri
Department of Neuropathology
Radcliff Infirmary
Oxford OX2 6HE, UNITED KINGDOM

Steven H. Ferris, Ph.D.
New York University School of Medicine
550 First Avenue
New York, New York 10016

Dr. Caleb E. Finch
Andrus Gerontology Center

University of Southern California
University Park
Los Angeles, California 90024

Dr. Richard S. J. Frachowiak
National Hospital for Nervous Diseases
London, UNITED KINGDOM

Dr. Paula Fuld
Department of Neurology
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, New York 10461

Pierluigi Gambetti, M.D.
Institute of Pathology
Case Western Reserve University
2085 Adelbert Road
Cleveland, Ohio 44106

Dr. Samuel Gershon
Department of Psychiatry
Wayne State University School of Medicine
540 East Canfield
Detroit, Michigan 48207

Dr. George G. Glenner
Department of Pathology
University of California School of Medicine
225 Dickinson Street
San Diego, California 92103

Patricia Goldman-Rakic, Ph.D.
Section of Neuroanatomy
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

Dr. C. -G. Gottfries
Department of Psychiatry
St. Jörgens Sjukhus
Hisings Backa S433 03, SWEDEN

John Growdon, M.D.
Department of Neurology ACC-7
Massachusetts General Hospital
32 Fruit Street
Boston, Massachusetts 02114

Dr. James S. Gusella
Neurology Department and Genetics Unit

Massachusetts General Hospital
Boston, Massachusetts 02114

Dr. Leonard L. Heston
Department of Psychiatry
University of Minnesota Medical School
Box 511 Mayo Memorial Building
420 Delaware Street SE
Minneapolis, Minnesota 55455

Dr. Albert Heyman
Division of Neurology
Duke University Medical Center
Post Office Box 3813
Durham, North Carolina 27710

Oleh Hornykiewicz, M.D.
Institution of Biochemical Pharmacology
University of Vienna
Borschkegasse 8a
Vienna A-1090, AUSTRIA

Leslie L. Iversen, Ph.D.
Neuroscience Research Center
Merck, Sharp & Dohme Limited
Terlings Park near Harlow
Essex EN11 9BU, UNITED KINGDOM

Dr. Joseph Jankovic
Department of Neurology
Baylor College of Medicine, Texas Medical Center
Houston, Texas 77030

Richard T. Johnson, M.D.
Department of Neurology
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205-2182

Eric R. Kandel, M.D.
Columbia University, CPS
Center of Neurobiology and Behavior
722 West 168th Street
New York, New York 10032

Dr. I. Karlsson
Department of Psychiatry
St. Jörgens Sjukhus
Hisings Bacaka S 433 03, SWEDEN

Dr. David Kuhl
University of California
710 Westwood Boulevard
Los Angeles, California 90024

Dr. Leonard Kurland
Department of Medical Statistics and Epidemiology
Mayo Clinic
Rochester, Minnesota 55905

Dr. J. William Langston
Department of Neurology
Santa Clara Valley Medical Center
San Jose, California 95128

Raymond J. Lasek, Ph.D.
Laboratory of Molecular Neuroarchitectonics
Case Western Reserve University School of Medicine
Department of Developmental Genetics and Anatomy
2119 Abington Road
Cleveland, Ohio 44106

Charles A. Marotta, M.D., Ph.D.
Departments of Psychiatry and Biochemistry
Harvard Medical School, Mailman Research Center
McLean Hospital
Belmont, Massachusetts 02178

Dr. C. David Marsden
University Department of Neurology
and Parkinson's Disease Society Research Centre
Institute of Psychiatry & Kings College
Hospital Medical School
Denmark Hill
London SE5, UNITED KINGDOM

Joseph B. Martin, M.D., Ph.D.
Department of Neurology
Harvard Medical School
Massachusetts General Hospital
Fruit Street
Boston, Massachusetts 02114

Colin Masters, M.D.
Department of Neuropathology
Royal Perth Hospital
Box X 2213
G.P.O., Perth, WESTERN AUSTRALIA

Richard Mayeux, M.D.
Department of Neurology

Columbia University
CPS, 710 West 168th Street
New York, New York 10032

John Z. Mazziotta, M.D., Ph.D.
Department of Neurology
UCLA Medical Center
Reed Neurological Institute
760 Westwood Plaza
Los Angeles, California 90024

Marek-Marsel Mesulam, M.D.
Behavioral Neurology Unit
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02215

Dr. C. Q. Mountjoy
Department of Psychatry
Addenbrooke's Hospital
Cambridge CB2 2QQ, UNITED KINGDOM

Dr. Charles B. Nemeroff
University of North Carolina School of Medicine
Chapel Hill, North Carolina 27514

Alan Peters, Ph.D.
Department of Anatomy
Boston University School of Medicine
80 East Concord Street
Boston, Massachusetts 02118

Dr. T. P. S. Powell
Department of Human Anatomy
Oxford University
South Park's Road
Oxford OX1 3QX, UNITED KINGDOM

Richard W. Price, M.D.
Department of Neurology
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

Stanley B. Prusiner, M.D.
Department of Neurology
M-794
University of California School of Medicine
San Francisco, California 94143

Marcus Raichle, M.D.
Washington University School of Medicine
Department of Neuroradiology
660 South Euclid Avenue, Box 8131
St. Louis, Missouri 63110

Dr. Stanley I. Rapoport
National Institutes of Health, Laboratory of Neurosciences
NIA Building 10, Room 6C103
9000 Rockville Pike
Bethesda, Maryland 20205

Thomas S. Reese, M.D.
Marine Biology Laboratory
Woods Hole, Massachusetts 02543

Dr. Martin Rossor
Department of Neurology
King's College Hospital
Denmark Hill
London SE5 9RS, UNITED KINGDOM

Dr. Martin Roth
Department of Psychiatry
University of Cambridge Clinical School
Level 4, Addenbrooke's Hospital
Hills Road 3
Cambridge, CB2 2QQ, UNITED KINGDOM

Dennis J. Selkoe, M.D.
Ralph Lowell Laboratories
Mailman Research Center
Harvard Medical School
McLean Hospital
Belmont, Massachusetts 02178

John R. Sladek, Jr., Ph.D.
Departments of Neurobiology and Anatomy
The University of Rochester Medical Center
School of Medicine and Dentistry
Box 603, 601 Elmwood Avenue
Rochester, New York 14642

Ira Shoulson, M.D.
Department of Neurology
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, New York 14642

Dr. Leon J. Thal
Department of Neurology

Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, New York 10461

Stanley J. Watson, Jr., M.D., Ph.D.
University of Michigan School of Medicine
Mental Health Research Institute
Ann Arbor, Michigan 48109

Nancy S. Wexler, Ph.D.
Hereditary Disease Foundation
606 Wilshire Boulevard, Suite 504
Santa Monica, California 90201

Dr. Bengt Winblad
Department of Pathology
University of Umea
Umea S 901 87. SWEDEN

Henry M. Wisniewski, M.D., Ph.D.
Institute for Basic Research in Developmental Disabilities
1050 Forest Hill Road
Staten Island, New York 10314

Krystyna Wisniewski, M.D.
Institute for Basic Research in Developmental Disabilities
1050 Forest Hill Road
Staten Island, New York 10314

Dr. Shu-Hui Yen
Department of Pathology
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, New York 10461

Anne B. Young, M.D.
Neurosciences Laboratory Building
University of Michigan
1103 East Huron Street
Ann Arbor, Michigan 48103

IV. RESEARCH PROPOSALS: BACKGROUND, HYPOTHESIS, PREPARATION, REVIEW, AND FUNDING

The genesis of a funded research proposal is a time-consuming, sometimes painful, multistep process. The investigator-initiated R01 (an individual research grant) is the most important type of federal support in neuroscience. Other grants provide training for young investigators or help these new investigators to initiate independent research projects. For example, institutional training grants provide support for young physicians and scientists, and awards such as the Clinical-Investigator Development Award, Physician-Scientist Award, etc., are designed to help new investigators develop independent programs of research. Needs also exist for other types of research funding. Outstanding Program Project Grants should be supported because these types of proposals usually support multidisciplinary studies involving basic and clinical neuroscience, and their format strongly encourages interactions among investigators using different approaches to study a given series of related problems. In addition, Center Grants targeted for specific problems (e.g., Alzheimer's Disease Research Centers, Centers for the Study of Mental Retardation, Centers for Research on Huntington's Disease, etc.) can be extremely productive mechanisms of funding scientific approaches focused on specific types of human disease. Thus, a variety of types of granting mechanisms are available but, unfortunately, the levels of funding, at present, are not adequate to support many of the important research projects generated in the minds of contemporary neuroscientists.

In the paragraphs below, I have tried to outline some of the key features of the production of a research grant and have commented upon the review process as well as mechanisms and problems of funding.

Background of Potential Investigators

A critical component of the grant proposal process is the training of young physicians and scientists who will eventually develop new ideas and new approaches for the study of brain function. Thus, our society must realize that resources must be allocated for such training. Only a trained investigator is in a position to think creatively about problems of the nervous system. Many physicians and basic scientists elect to spend several postdoctoral years working in the laboratory of a senior investigator under whom they broaden and deepen their conceptual background and learn how to design critical experiments and use new technical approaches. First-class pre- and postdoctoral training prepares the groundwork for the genesis of new research projects. In the majority of instances, the trainee will pursue research in an area to which he has been exposed during his pre- or postdoctoral training.

Hypothesis

The second step in this process is the generation of a new idea, which is usually the result of a complex series of processes that includes theoretical discussions, laboratory work, and a reading of the literature. From this series of parallel pursuits, a hypothesis is developed. The investigator must then ask himself a series of questions. Is the hypothesis testable using currently available methods? Must new approaches be devised? Can the experiment be designed to result in an unequivocal answer? If the answers to the above questions are "yes", the investigator conducts preliminary experiments to test aspects of this hypothesis. If preliminary studies are encouraging, the investigator needs to obtain support for the research project. In the majority of instances, adequate support from local sources is not available, and the investigator must apply to federal agencies (e.g., the NIH) for grant support. Therefore, the investigator begins to prepare an R01 application, i.e., an investigator-initiated research proposal.

Preparation of a Grant Application

Ideas must be developed and concepts and approaches supported by preliminary studies and work cited in the literature. Thus, long before the grant is submitted for review, the investigator must commit a substantial amount of personal energy as well as available technical and secretarial help to the development and preparation of a grant proposal. Once the proposal has been written, many investigators circulate the draft to selected colleagues for their comments. Eventually, the proposal document is produced in a format appropriate for consideration by the NIH. The investigator-initiated R01 has several components, which are usually arranged in the following format. Section I includes the Abstract, Personnel, Budgets, Biographical Sketch(es), and Resources & Environment. Section II is the Research Plan, including Specific Aims, Significance, Preliminary Studies, Experimental Design & Methods, and Literature Cited. This document is then submitted in multiple copies to the NIH.

Grant Review

The grant application is initially received and reviewed by the Division of Research Grants of the NIH. This agency triages applications to Study Sections (a body of 15-20 established scientists who are recognized experts in the field). The application is usually assigned to two primary reviewers, two secondary reviewers, and one or two readers. Each reviewer independently assesses the grant application and, at Study Section meetings (held three times annually), the primary reviewers, secondary reviewers, and readers discuss the proposal before the other members of the Study Section. Having my own grants reviewed by Study Sections and having served as a Member and, subsequently, as Chairman of the Neurology A Study Section, I can testify to the rigor and integrity of this review process. At the end of the discussion of each proposal, the application is approved or disapproved. If approved, members of the Study Section are requested to assign the proposal a priority score ranging from "100" (best) to "500" (poorest).

On the basis of Study Section scores, the NIH staff decides which of the approved grants will be funded. Many excellent proposals achieve scores between 130 and 160. Unfortunately, because of changes in funding patterns, the funding cutoff falls between 135 and 145. Since it is virtually impossible to truly discriminate differences in quality between 130 and 160, many excellent grant applications are not funded. Thus, it is now much more difficult for investigators to obtain adequate funds to pursue new ideas. This is a discouraging state of affairs for promising young scientists who have been well trained in excellent institutions and are now ready to make creative contributions to neuroscience.

Grant Funding

At current levels, approximately 25% of approved neuroscience proposals are awarded funds from the NIH, with the National Institute of Neurological and

Communicative Disorders and Stroke (NINCDS) and the National Institute on Aging (NIA) the major institutes providing financial support for these investigations. Some of these grants are funded in full for five years, but the majority suffer cuts in budgets and duration of support. It is important to emphasize that the majority of proposals are not funded. Difficulties described above can have more subtle effects beyond whether the proposal is funded or not. For example, with available funding so highly restricted, investigators are sometimes reluctant to write grant proposals that outline research approaches that have enormous potential but may be criticized by reviewers as too risky or too imaginative. This perception can actually serve to stifle creative thought. Thus, at present, there are extraordinary opportunities in contemporary neuroscience, but the allocation of resources in this field falls far short of what is needed by the many excellent investigators working on problems of the brain.

Conclusion

Although scientific research is a highly rewarding pursuit, the grant process is, for many investigators, very frustrating, as all too few excellent research grants are funded. If we are to reap the benefits of neuroscience (i.e., advances in understanding and treating human neurological disease), our society must be willing to commit more resources to the exciting and challenging field of neuroscience.